CHAPTER IV

RESULTS AND DISCUSSION

1. Characteristics of Patients

Summary of the characteristics of the patients receiving every 8 hour treatment and once-daily treatment are presented in table 4.1. 102 patients enrolled in the study but only 92 patients were selected for matching. The 46 patients in the every 8-hour treatment group were 30 females and 16 males, they were ranging in age from 18 to 90 years (mean = 45.3; SD = 18.1). The 46 patients in the once-daily treatment group consisted of 30 females and 16 males ranging in age from 17 to 94 years(mean = 47.2; SD = 21.4).(See figure 4.1 and 4.2)

The mean weights of the patients in the every 8-hour treatment group and the once-daily treatment group were 52.5 ± 10.4 and 51.4 ± 8.9 kilograms, respectively (figure 4.3). The mean of prescribed dosages by physicians was 3.56 ± 0.51 mg/kg for the every 8 hour treatment group which was equal to 3.56 ± 0.49 mg/kg for the once-daily treatment group (figure 4). Indications for gentamicin treatment were urinary tract infection (35 %), fever of undetermined origin (11 %), septic arthritis (7 %), sepsis (9 %), febrile neutropenia (4 %), cellulitis (4 %), pneumonia (9 %), wound infection (2 %), infectious diarrhea (2 %) and infective endocarditis (17 %) (figure 4.5). The means of initial serum creatinine were 1.2 ± 0.3 mg/dl for the patients in the every 8-hour treatment group and 1.0 ± 0.3 mg/dl for the patients in the once-daily treatment group (figure 4.6). The mean initial creatinine clearance for the every 8-hour treatment group and the once-daily treatment group were 59.6 ± 25.7 ml/min and 62.3 ± 30.0 ml/min, respectively. In this study, we tried to match sex, age, weight, dose, indication, severity of disease, initial serum creatinine and creatinine clearance of both groups of patients. However,for short term study, it is not easy to match patients appropriately in all aspects, therefore , some aspects were not absolutely matched which might be the

weak point of this study, so we had tried to match as many appropriate pairs as possible.

Additionally, Regarding the severity of the disease, the cases with the same disease and equal initial severity level were matched. Actually, the best design for this type of study is to sampling patients receiving gentamicin administation by a randomized, double blind unmatched case control method. However, the physicians might disagree and feel uncomfortable so we decided to observe.

In this study, we have monitored 30 pairs of females and 16 pairs of males. The number of females were higher than males so further clinical studies are needed to investigate in the similar number of male and female patients.

Table 4.2 showed clinical responses of both groups. 29 patients in every 8-hour treatment and 40 patients in once-daily treatment group showed improved outcome. Excluded duration of treatment of the patients without good response, the mean duration of treatment was 13.2 ± 3.5 day the every 8-hour treatment group while the mean duration of treatment was 8.3 ± 4.0 day in once-daily treatment group. 9 patients in every 8-hour treatment group had developed nephrotoxicity while 5 patients in once-daily treatment group had eveloped nephrotoxicity,respectively. For dosage adjustment,19 patients in 8-hour treatment group required new dosage regimen while 6 patients in once-daily treatment required new dosage regimen. Only one patient with infective endocarditis (No. 44) in the every 8-hour treatment complained about hearing loss caused by synergistic ototoxicity between gentamicin and furosemide that may occur in patient with prolong treatment. In this study , 3 patients were dead , 2 of them died from sepsis and one of them died from respiratory failure.

After finished the course of treatment or the patients showed good clinical response, the patients were discharged or switched to oral antibiotics such as ampicillin , amoxycillin , norfloxacin , cefachlor , cefalethin or the less nephrotoxicity antibiotics.

Table 4.1 Characteristics of the patients receiving every 8-hour treament and once-daily treatment.

No	Sex	Age (yr)	Weight (kg)	Dose (mg/kg)	Indication	No	Sex	Age (yr)	Weight (kg)	Dose (mg/kg)	Indication
1	f	61	45	4.0	UTI	1a	f	70	48	4.2	UTI
2	f	31	58	3.1	UTI	2a	f	28	54	3.0	UTI
3	f	67	33	4.5	UTI	3a	f	72	43	4.1	UTI
4	f	52	47	2.6	UTI	4a	f	73	40	2.5	UTI
5	f	47	55	2.7	UTI	5a	f	60	48	2.5	UTI
6	f	41	55	4.0	UTI	6a	f	32	60	4.0	UTI
7	f	68	45	4.0	UTI	7a	f	70	40	4.0	UTI
8	f	60	46	3.9	UTI	8a	f	57	41	3.9	UTI
9	f	78	40	3.0	UTI	9a	f	80	41	3.0	UTI
10	f	90	42	2.9	UTI	10a	f	75	45	3.1	UTI
11	f	70	58	3.1	UTI	11a	f	82	50	3.2	UTI
12	f	59	46	3.9	UTI	12a	f	64	42	4.3	UTI
13	f	69	65	3.2	UTI	13a	f	76	54	3.0	UTI
14	m	28	62	3.0	UTI	14a	m	30	53	3.0	UTI
15	m	25	48	3.8	UTI	15a	m	27	42	3.8	UTI
16	m	23	53	4.0	UTI	16a	m	17	60	4.0	UTI
17	f	29	45	4.0	FUO	17a	f	29	42	3.8	FUO
18	f	30	63	2.9	FUO	18a	f	42	70	2.9	FUO
19	f	27	60	3.0	FUO	19a	f	20	72	3.3	FUO
20	m	32	62	3.0	FUO	20a	m	41	65	3.1	FUO

Continued.....

No	Sex	Age (yr)	Weight (kg)	Dose (mg/kg)	Indication	No	Sex	Age (yr)	Weight (kg)	Dose (mg/kg)	Indication
21	m	35	60	3.0	FUO	21a	m	31	58	2.8	FUO
22	f	62	45	4.7	Septic arthritis	22a	f	64	42	4.3	Septic arthritis
23	f	66	48	3.8	Septic arthritis	23a	f	94	36	3.9	Septic arthritis
24	m	53	69	3.9	Septic arthritis	24a	f	75	40	4.0	Septic arthritis
25	f	66	45	4.0	Wound infection	25a	m	36	60	4.0	Wound infection
26	f	58	45	4.0	Sepsis	26a	f	67	42	3.8	Sepsis
27	f	30	42	4.3	Sepsis	27a	f	24	38	4.0	Sepsis
28	f	30	42	4.3	Sepsis	28a	f	27	55	4.4	Sepsis
29	m	73	42	4.3	Sepsis	29a	m	67	35	4.0	Sepsis
30	f	20	61	3.0	Febrile neutropenia	30a	f	18	65	3.0	Febrile neutropenia
31	m	31	70	2.6	Febrile neutropenia	31a	m	40	75	2.7	Febrile neutropenia
32	f	32	44	4.1	Cellulitis	32a	f	27	38	4.2	Cellulitis
33	f	50	57	3.7	Cellulitis	33a	f	45	42	3.8	Cellulitis
34	f	48	60	3.0	Pneumonia	34a	f	67	57	2.9	Pneumonia
35	m	36	54	3.3	Pneumonia	35a	m	30	55	3.6	Pneumonia
36	m	28	70	3.4	Pneumonia	36a	m	24	68	3.5	Pneumonia
37	m	60	45	3.3	Pneumonia	37a	m	66	55	3.3	Pneumonia
38	f	22	52	4.6	Infectious diarrhae	38a	f	19	50	4.8	Infectious diarrhae
39	f	18	52	4.6	IE	39a	f	19	50	4.8	IE
40	f	35	57	3.7	IE	40a	f	30	60	3.5	IE
41	f	39	50	3.6	IE	41a	f	35	57	3.5	IE
42	m	35	50	3.6	IE	42a	m	42	56	3.6	IE

Continued.....

No	Sex	Age (yr)	Weight (kg)	Dose (mg/kg)	Indication	No	Sex	Age (yr)	Weigh t (kg)	Dose (mg/kg)	Indication
43	m	43	54	2.8	IE	43a	m	51	57	3.1	IE
44	m	49	50	3.0	IE	44a	m	52	47	3.2	IE
45	m	50	55	3.3	IE	45a	m	47	51	3.2	IE
46	m	26	70	3.4	IE	46a	m	30	67	3.6	IE
Mean		45.3 ±15.7	52.5 ±7.5	3.56 ±0.51		Mean		47.2 ±1 9.0	51.4 ±8.8	3.56 ±0.49	

Table 4.2 Clinical responses of the patients receiving every 8-hour treatment and once daily treatment.

No	Efficacy	Duration (day)	Nephro-toxicity	Dosage adjustment	No	Efficacy	Duration (day)	Nephro-toxicity	Dosage adjustment
1	y	14	y	y	1a	y	8	y	y
2	y	14	y	y	2a	y	8	y	y
3	y	15	n	y	3a	y	5	n	n
4	y	10	n	n	4a	y	9	n	n
5	y	11	n	n	5a	y	3	n	n
6	y	7	n	y	6a	y	5	n	n
7	y	11	y	y	7a	y	5	n	n
8	y	16	y	y	8a	y	8	n	y
9	n	3	n	n	9a	y	6	n	n
10	n	4	n	n	10a	y	4	n	n
11	n	12	n	n	11a	y	10	n	n
12	y	14	n	n	12a	y	3	n	n
13	y	11	n	n	13a	n	13	n	n
14	n	8	n	n	14a	y	4	n	n
15	y	11	y	y	15a	y	10	n	n
16	n	6	n	y	16a	y	7	n	n
17	n	12	n	n	17a	y	13	n	n
18	n	6	n	y	18a	y	3	n	n
19	y	7	n	y	19a	y	4	n	n
20	n	7	n	n	20a	y	8	n	n

Continued.....

No	Efficacy	Duration (day)	Nephro-toxicity	Dosage adjustment	No	Efficacy	Duration (day)	Nephro-toxicity	Dosage adjustment
21	n	10	n	n	21a	y	13	n	n
22	y	14	n	n	22a	y	12	n	n
23	y	13	n	n	23a	y	3	n	n
24	y	17	n	y	24a	y	5	n	n
25	y	9	n	n	25a	y	9	n	n
26	n	17	n	n	26a	y	9	n	n
27	y	14	n	n	27a	y	16	n	n
28	n	15	n	n	28a	y	8	n	n
29	n	14	n	n	29a	y	10	n	n
30	n	17	n	y	30a	y	8	n	n
31	n	7	n	n	31a	y	9	n	n
32	n	16	n	y	32a	n	10	n	n
33	y	10	n	n	33a	y	4	n	n
34	y	10	n	n	34a	y	3	n	n
35	y	11	n	n	35a	y	7	n	n
36	y	14	n	n	36a	y	11	n	n
37	y	12	n	n	37a	y	7	n	n
38	y	15	n	n	38a	y	14	n	n
39	y	14	n	y	39a	y	14	y	y
40	n	23	n	y	40a	y	14	n	n
41	y	20	y	y	41a	n	8	n	n
42	y	16	n	n	42a	n	3	n	n

Continued.....

No	Efficacy	Duration (day)	Nephro - toxicit y	Dosage adjustment	No	Efficacy	Duration (day)	Nephro-toxicity	Dosage adjustment
43	y	23	y	y	43a	y	15	y	y
44	n	36	y	y	44a	y	17	y	y
45	y	15	y	n	45a	y	10	n	n
46	y	15	n	y	46a	n	10	n	n
Total	29		9	19	Total	40		5	6

Figure 4.1 Number of male and female patients in the every 8-hour treatment group and the once daily treatment group

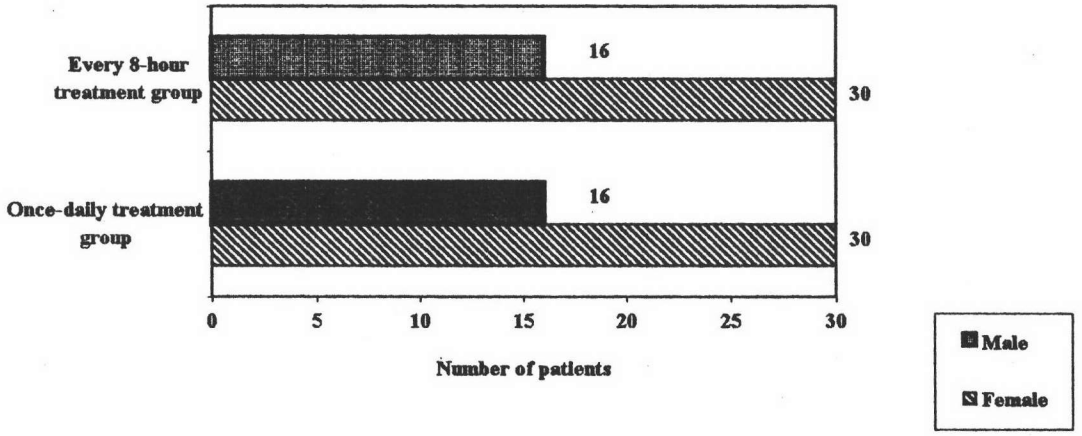


Figure 4.2 Comparison age between the every 8-hour treatment group and the once-daily group.

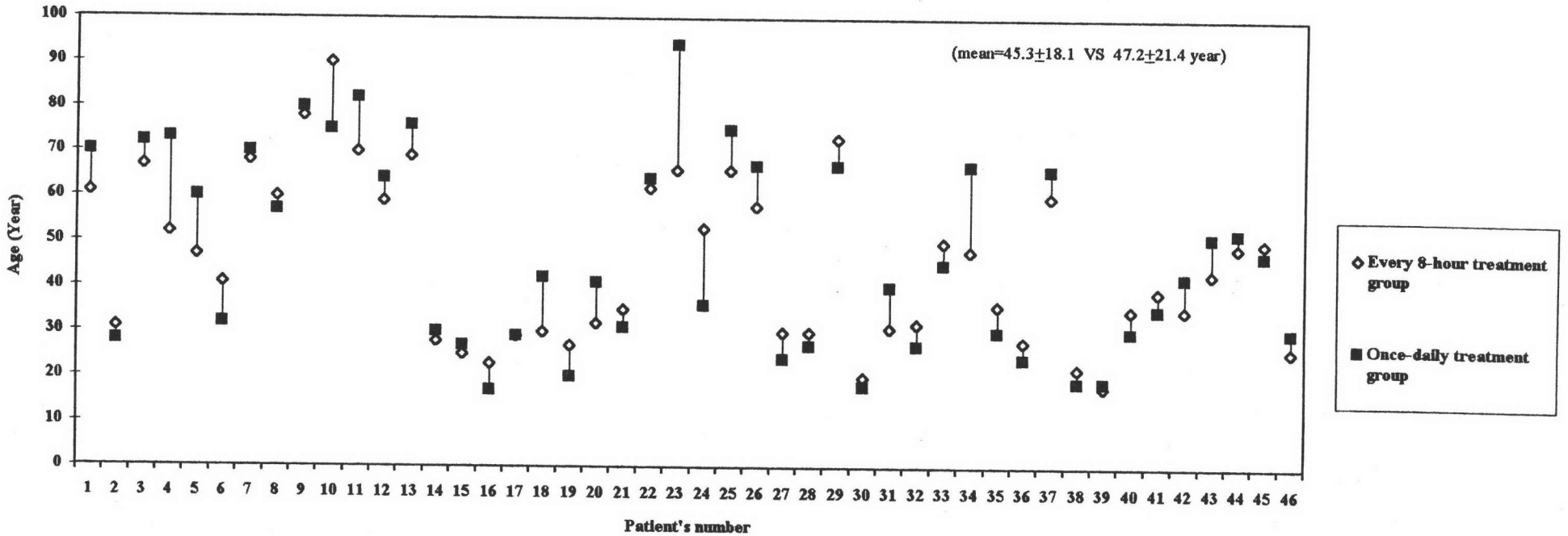


Figure 4.3 Comparison body weight between the every 8-hour treatment group and the once-daily treatment group.

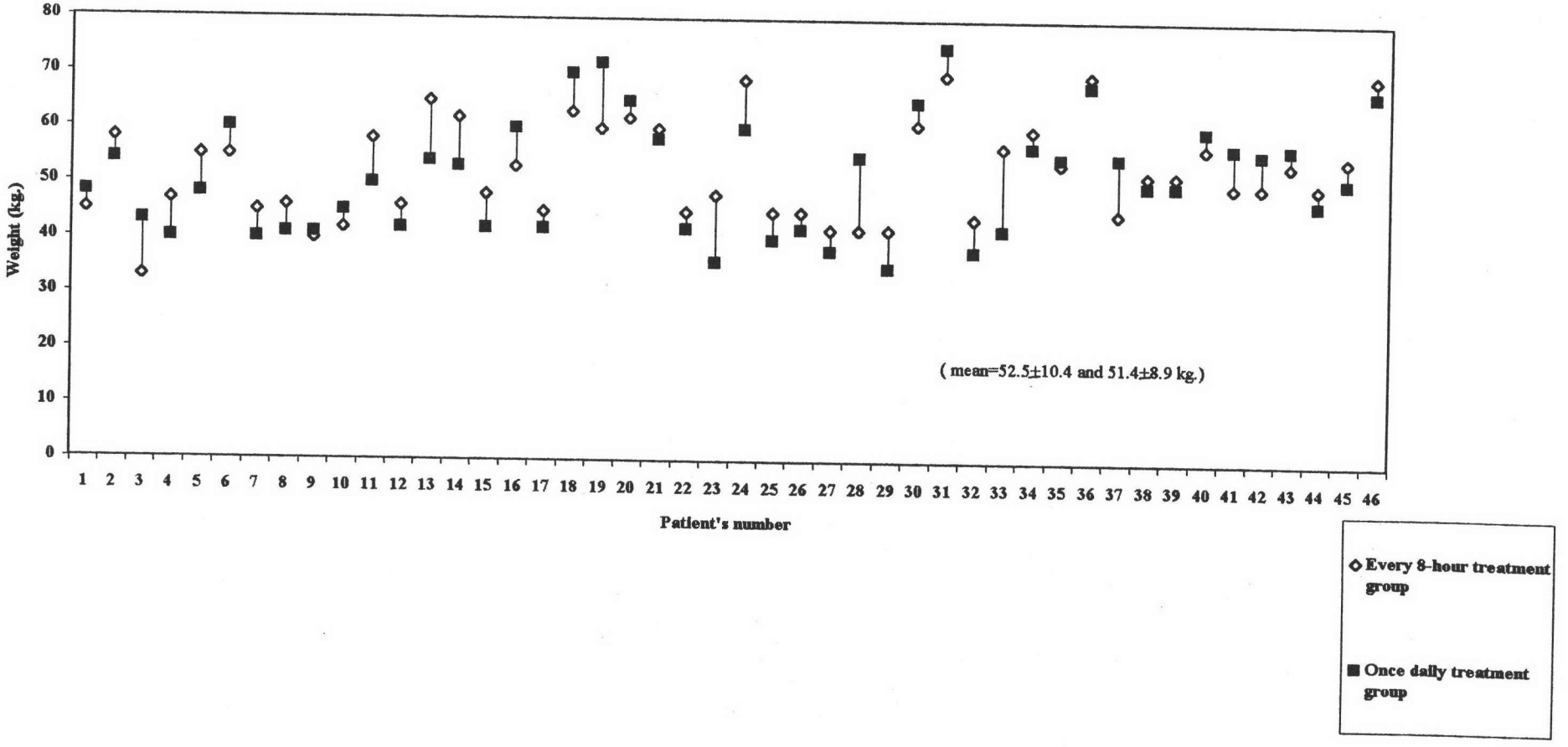


Figure 4.4 Comparison the prescribed dosage of gentamicin between the every 8-hour treatment group and once-daily treatment group.

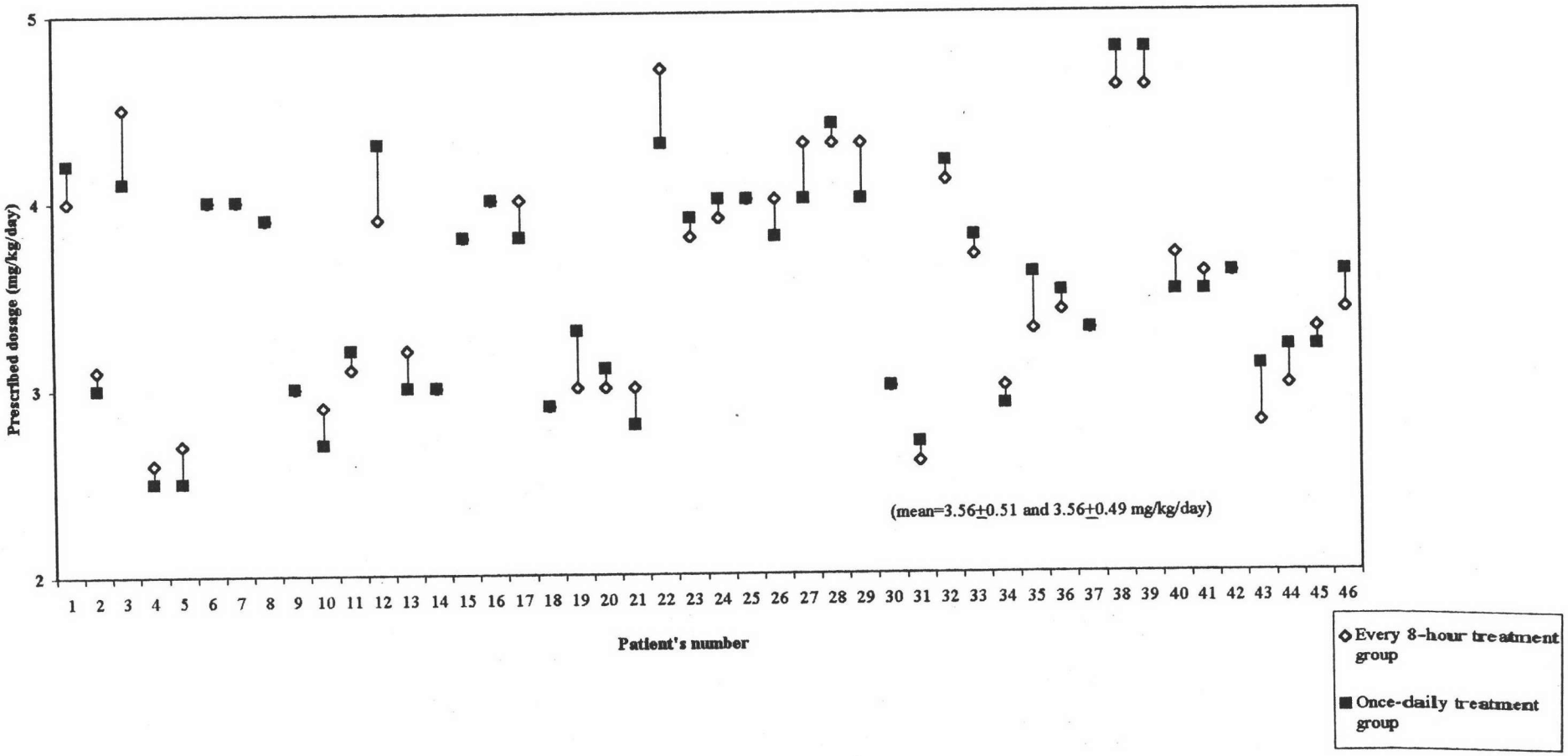


Figure 4.5 Summary of indication for gentamicin treatment

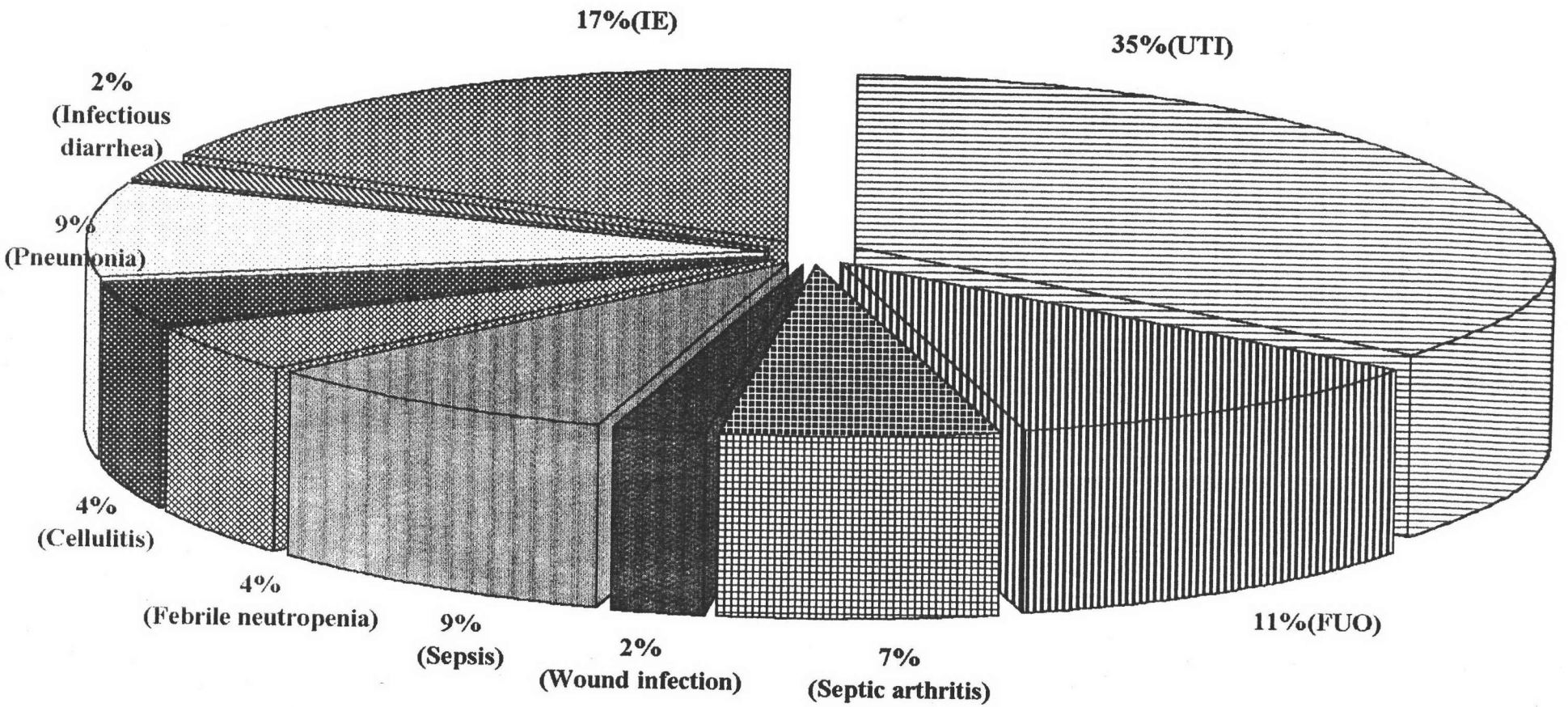


Figure 4.6 Comparison of the initial serum creatinine between the every 8-hour treatment group and the once-daily treatment group.

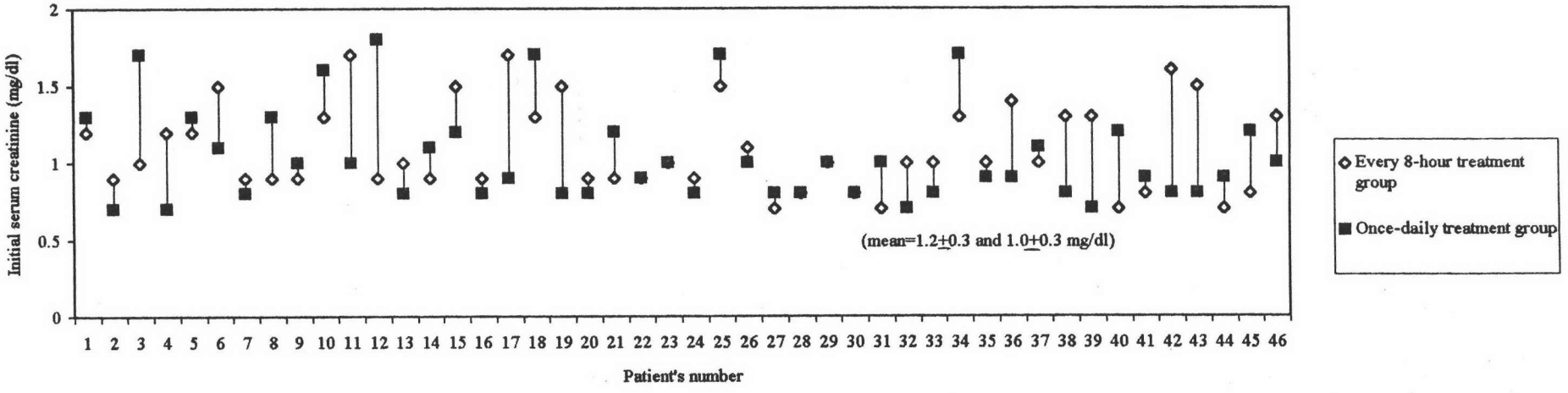
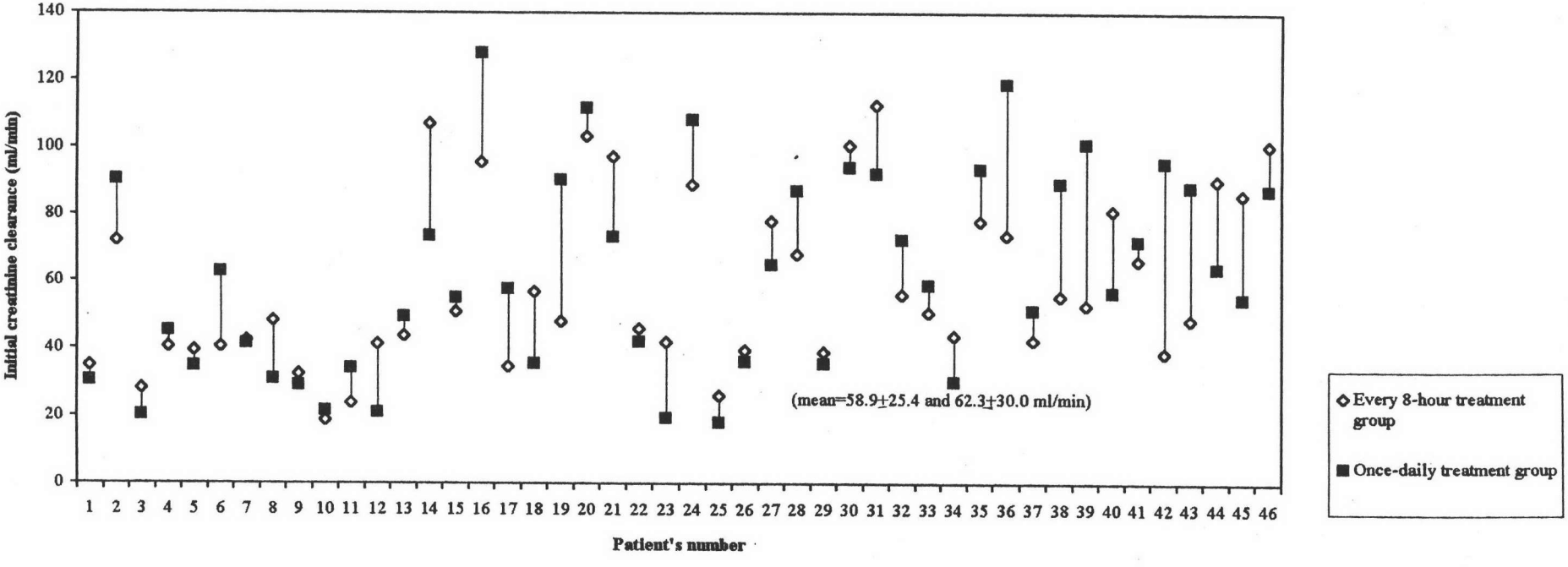


Figure 4.7 Comparison of the initial creatinine clearance between the every 8-hour treatment group and the once-daily treatment group.



2. Efficacy

Twenty-nine out of forty-six patients (63 %) of the every 8-hour treatment group showed the improved outcome while forty out of forty-six patients (87 %) of the once-daily treatment group showed improvement. This result indicated that gentamicin with once-daily treatment might have higher efficacy than gentamicin with every 8-hour treatment , $p < 0.05$, as shown in table 4.3 and figure 4.8. The 3 criterias which we checked during the observation of the efficacy were body temperature, white blood cell count and culture sensitivity test. If these criteria were within normal limit , "good efficacy" will be record . Out of these criteria, we have recored " no efficacy". In some cases, if the culture sensitivity test was negative , white blood cell count was within normal limit , body temperature was higher than the normal limit and the physician interpreted as less efficacy or no efficacy in the last day of regimen , we recorded no efficacy. In some cases, the efficacy was also depended on the underlying disease which was regarded by the match case with the same underlying disease . We have monitored efficacy from the begining of administration until finishing the course of treatment. From this study, we have found that gentamicin showed effectiveness in some infection such as gram negative rod bacilli infection but in some other infectious diseases should be used in combined with other antibiotics for a more fruitful efficacy.

Once daily treatment showed higher efficacy than every 8-hour treatment in patients with UTI, FUO, sepsis, febrile neutropenia, as shown in table 4.4 and figure 4.9. For infective endocarditis, the cardiologists have recommended using gentamicin with every 8-hour treatment rather than once-daily treatment. Some physicians recently treat infective endocarditis with once daily gentamicin treatment which seems to have less efficacy than every 8-hour treatment.However,in this study, 5 out of 8 patients with infective endocarditis showed improvement with once daily regimen as compared to 6 out of 8 patients showed improvement in the 8-hour treatment group.

If the body temperature decreased to less than or equal to 37.5°c and the other criteria were within normal limit, it was classified as " good efficacy". If the body temperature was decreased but the final bopdy temperature was higher than 37.5°c, it was classified as " no efficacy". There was little different in body temperature of the patients who were recorded no efficacy in every 8-hour treatment group and once-daily treatment group but there was significant difference between every 8-hour treatment with good efficacy and once daily treatment with good efficacy in body temperature decrease since the fifth day (38.2 $\pm$ 0.5 ° c versus 37.8 $\pm$ 1.0 °c , $p < 0.05$), the sixth day (38.0 $\pm$ 0.62 °C versus 37.6 $\pm$ 0.7 °c , $p < 0.05$) and the seventh day (37.8 $\pm$ 0.7 °c versus 37.3 $\pm$ 1.0 °c , $p < 0.05$). These results indicated that the patients body temperature decreased faster after once-daily treatment than after every 8-hour treatment, as shown in figure 4.10.

Figure 4.11 showed white blood cell count decrease in the patients with every 8-hour treatment and once daily treatment classified by good efficacy and no efficacy. In no efficacy group, white blood cell count was showed little change from initial value but in good efficacy group , the values changed dramatically , however , there was significant difference in white blood cell decrease between every 8 hour treatment group with good efficacy and once daily treatment group with good efficacy measured on the fifth day (14.4 $\pm$ 3.2 cell*10^3/ml vs 10.0 $\pm$ 1.2 cell*10^3/ml) , the sixth day (14.0 $\pm$ 1.6 cell*10^3/ml vs 9.87 $\pm$ 2.6 cell*10^3/ml), the seventh day (10.7 $\pm$ 2.05 cell*10^3/ml vs 7.7 $\pm$ 2.1 cell*10^3/ml) , the eighth day (10.0 $\pm$ 2.6 cell*10^3/ml vs 7.0 $\pm$ 3.1 cell*10^3/ml) , the nineth day (9.9 $\pm$ 2.84 cell*10^3/ml vs 7.1 $\pm$ 0.9 cell*10^3/ml) and the tenth day (9.1 $\pm$ 1.46 cell*10^3/ml vs 7.0 $\pm$ 1.81 cell*10^3/ml) , $p < 0.05$. These results implied that efficacy on white blood cell count decrement in once-daily treatment group was better than in every 8-hour treatment group. Variable in underlying disease related to white blood cell such as cancer may have influence on this finding the white blood cell of some patients were decreased further if they were concomitantly treated with gentamicin and chemotherapy.

The difference of body temperature and white blood cell between the every 8-hour treatment group with good efficacy and the once-daily treatment group with good efficacy could be seen obviously since the fifth day after administration of gentamicin. These results confirmed that the once-daily treatment has presented the efficacy higher than the every 8-hour treatment.

Once daily treatment seemed to showed higher efficacy on ***Pseudomonas aeruginosa*** than every 8-hour treatment while every 8-hour treatment showed little higher efficacy on ***Streptococcus spp***. than once-daily treatment. There was no difference on efficacy with other micro-organisms between the two groups, as shown in table 4.5 and figure 4.12. These results indicated that once-daily treatment has no difference on antimicrobial efficacy from every 8-hour treatment ,excepted for ***Pseudomonas aeruginosa.***

Table 4.3 Comparison the efficacy between every 8-hour treatment and once-daily treatment.

Every 8-hour treatment		Once-daily treatment	
No.	Good Efficacy	No.	Good Efficacy
1	y	1a	y
2	y	2a	y
3	y	3a	y
4	y	4a	y
5	y	5a	y
6	y	6a	y
7	y	7a	y
8	y	8a	y
9	n	9a	y
10	n	10a	y
11	n	11a	y
12	y	12a	y
13	y	13a	n
14	n	14a	y
15	y	15a	y
16	n	16a	y
17	n	17a	y
18	n	18a	y
19	y	19a	y
20	n	20a	y

Continued.....

Every 8 hours treatment		Once daily treatment	
21	n	21a	y
22	y	22a	y
23	y	23a	y
24	y	24a	y
25	y	25a	n
26	n	26a	y
27	y	27a	y
28	n	28a	y
29	n	29a	y
30	n	30a	y
31	n	31a	y
32	n	32a	n
33	y	33a	y
34	y	34a	y
35	y	35a	y
36	y	36a	y
37	y	37a	y
38	y	38a	y
39	y	39a	y
40	n	40a	y
41	y	41a	n
42	y	42a	n

Continued.....

Every 8 hours treatment		Once daily treatment	
43	y	43a	y
44	n	44a	y
45	y	45a	y
46	y	46a	n
Total	29	Total	40
%	63.0	%	87.0

Figure 4.8 Comparison the efficacy between the every 8-hour treatment group and the once-daily treatment group by percentage of the patients with improved outcome

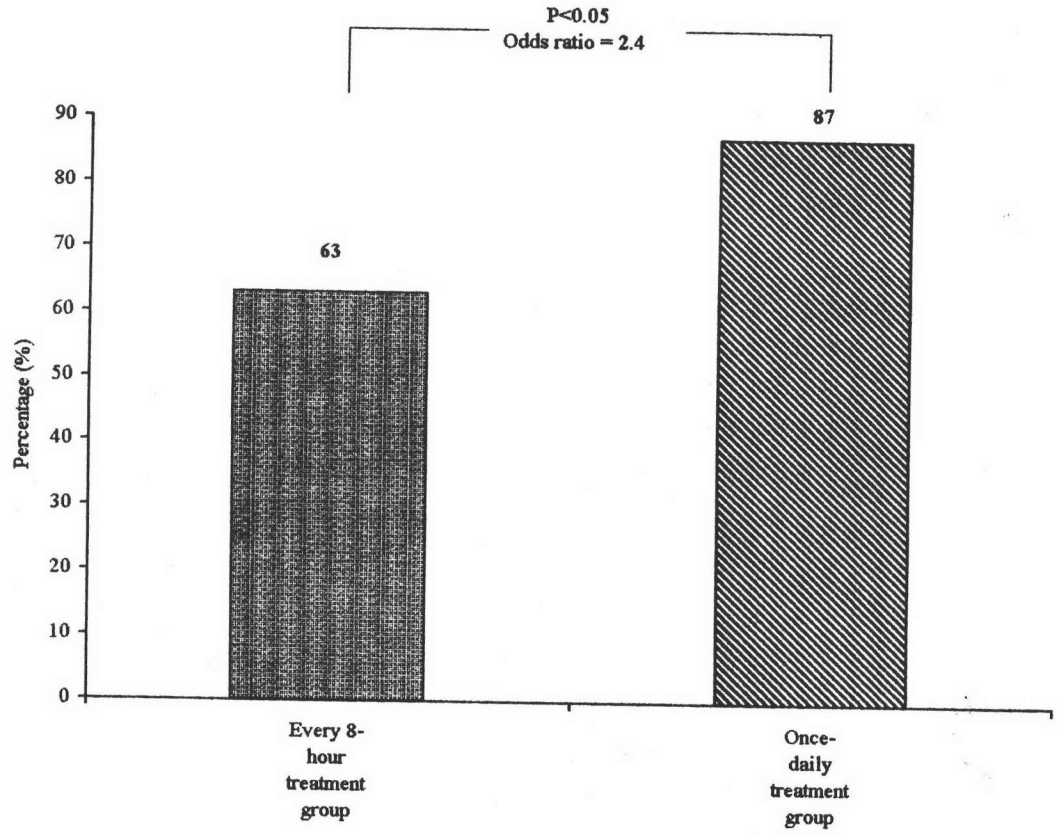


Table 4.4 Comparison the efficacy of gentamicin classified by infectious disease or febrile illness between every 8-hour treatment and once-daily treatment.

Indication	Every 8-hour treatment		Once daily treatment	
	Total	Good efficacy	Total	Good efficacy
1.Urinary tract infection	16	11	16	15
2.Fever of undetermined origin	5	1	5	5
3.Septic arthritis	3	3	3	2
4.Wound infection	1	1	1	1
5.Sepsis	4	1	4	4
6.Febrile neutropenia	2	0	2	2
7.Cellulitis	2	1	2	1
8.Pneumonia	4	4	4	4
9.Infectious diarrhea	1	1	1	1
10.Infective endocarditis	8	6	8	5
Total	46	29	46	40

Table 4.5 The efficacy of gentamicin on micro-organism in every 8-hour treatment group and once-daily treatment group.

Treatment	Every 8-hour treatment group		Once-daily treatment group	
Micro-organism	Total patients	Good efficacy	Total patients	Good efficacy
Acinetobacter baumanni	1	1	1	1
Enterococcus spp.	4	3	4	4
E. coli	5	3	5	4
Klebsiella spp.	6	5	5	5
Staphylococcus spp.	4	2	4	2
Streptococcus spp.	7	7	8	5
Salmonella spp.	1	1	1	1
Pseudomonas aeruginosa	2	0	3	3

Figure 4.9 Comparison of the efficacy clssified by indication between every 8-hour treatment and once-daily treatment .

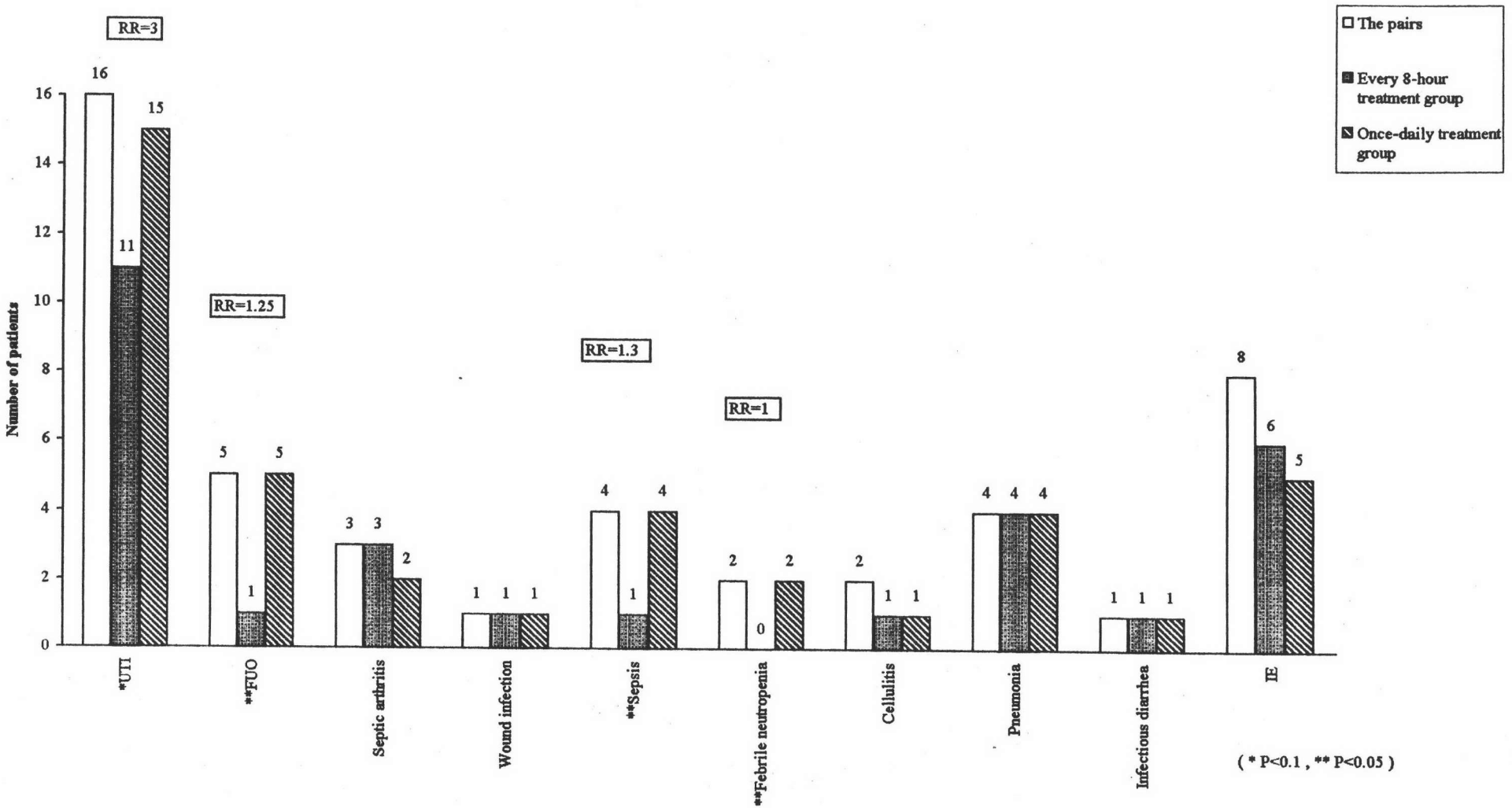


Figure 4.10 Comparison of the efficacy on body temperature between the every 8-hour treatment group and the once-daily treatment group.

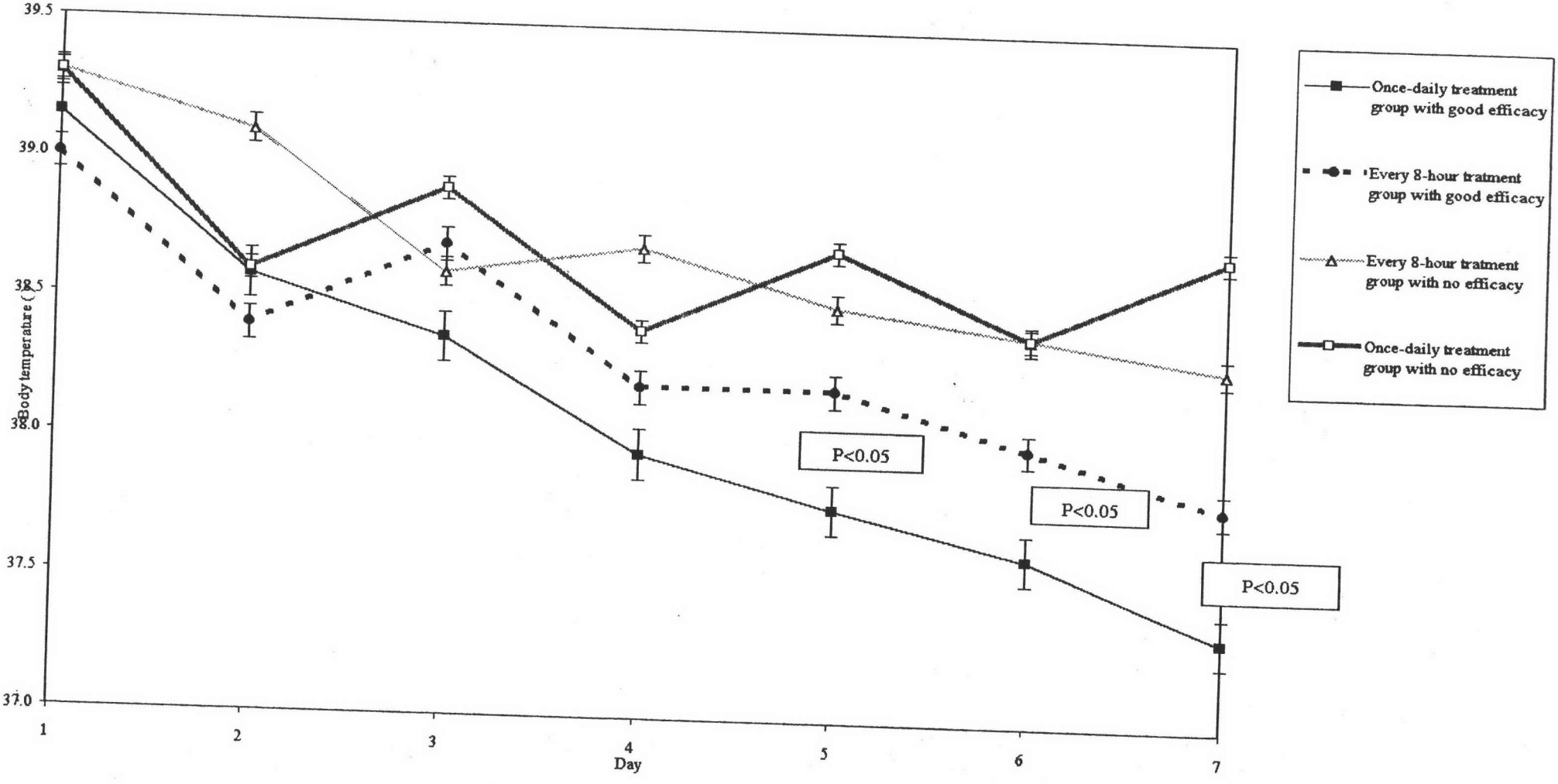


Figure 4.11 Comparison of the efficacy on white blood cell count decrement between the every 8-hour treatment group and the once-daily treatment group classified by good efficacy and no efficacy

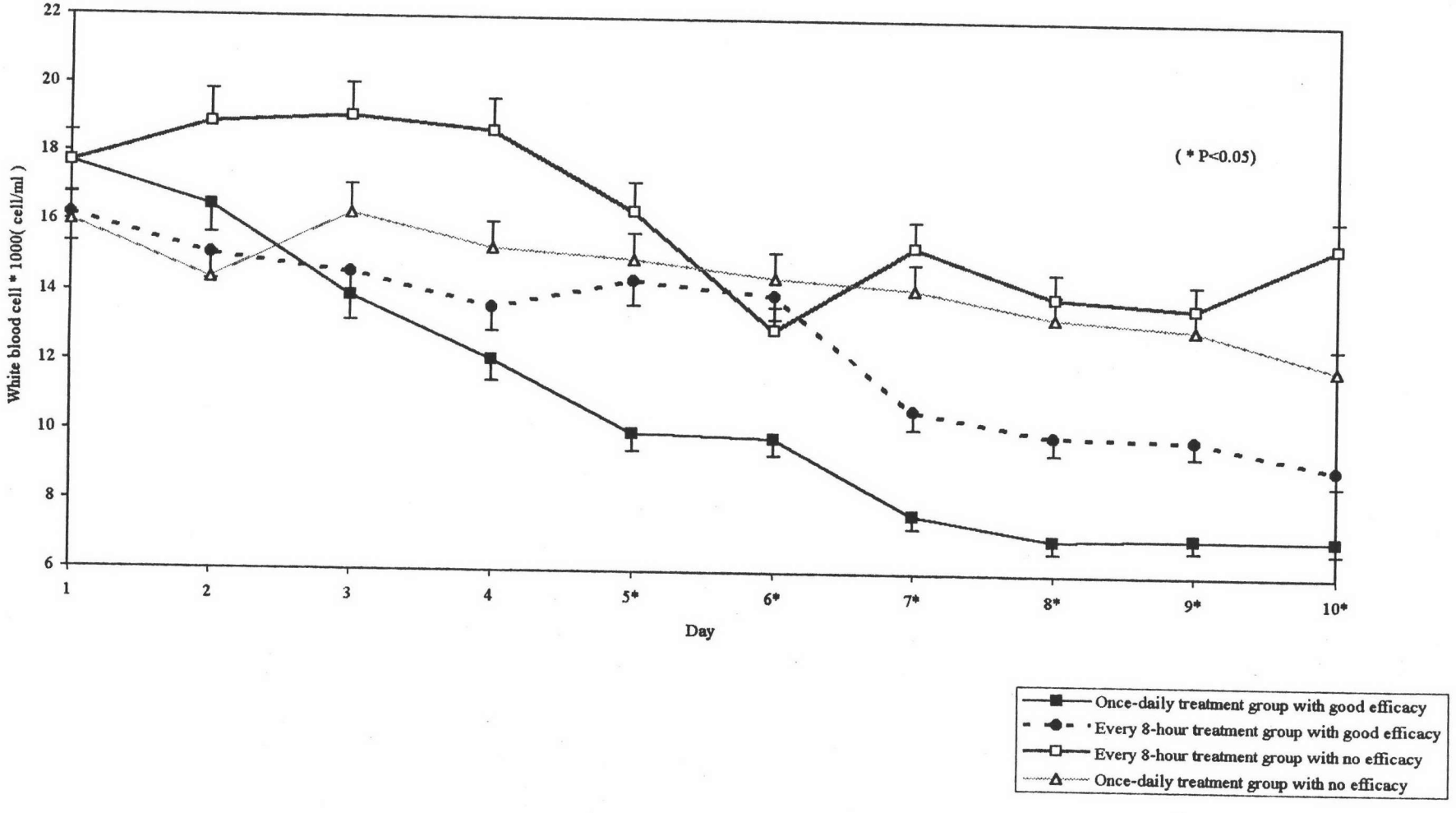
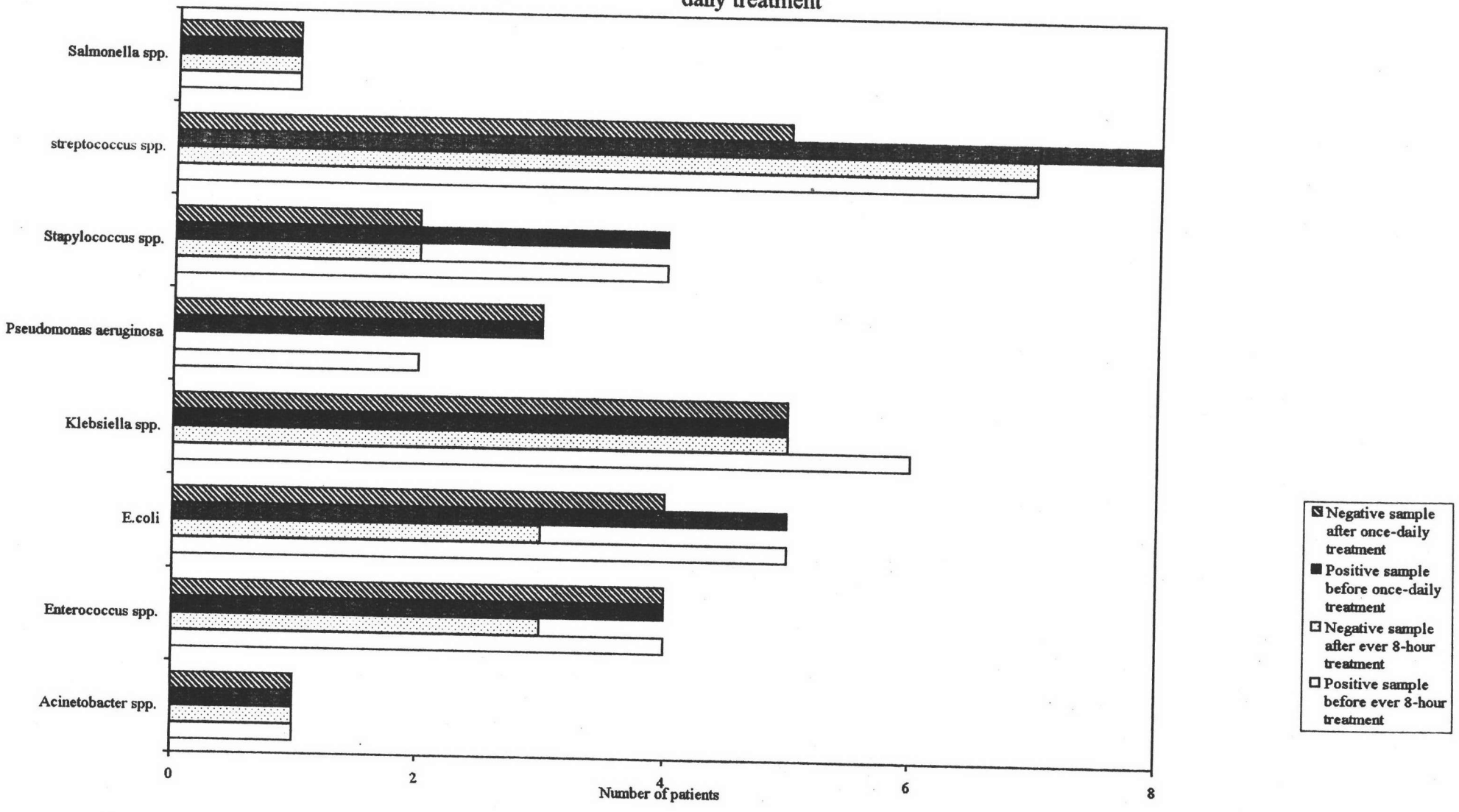


Figure 4.12 Presentration the efficacy of gentamicin on micro-organism classified by every 8-hour treatment and once-daily treatment



3. Duration

The duration of two treatments of both groups are shown in Table 4.6. The maximum duration of treatment was 36 days and the minimum was 3 days. Figure 4.13 showed that the duration of treatment was significantly less in the once daily treatment group as compared to the every 8-hour treatment group(8.3 ± 4.0 days vs 13.2 ± 3.5 days, $p < 0.05$). This finding indicates treatment with gentamicin on a once daily regimen seems to reduce health care costs and decrease hospitalization stay when compared with every 8-hour regimen.

Table 4.6 Comparison of the duration of treatment between the every 8-hour treatment group and the once daily treatment group.

Every 8- hour treatment group		Once-daily treatment group	
No.	Duration	No.	Duration
1	14	1a	8
2	14	2a	8
3	15	3a	5
4	10	4a	9
5	11	5a	3
6	7	6a	5
7	11	7a	5
8	16	8a	8
9	-	9a	6
10	-	10a	4
11	-	11a	10
12	14	12a	3
13	11	13a	-
14	-	14a	4
15	11	15a	10
16	-	16a	7

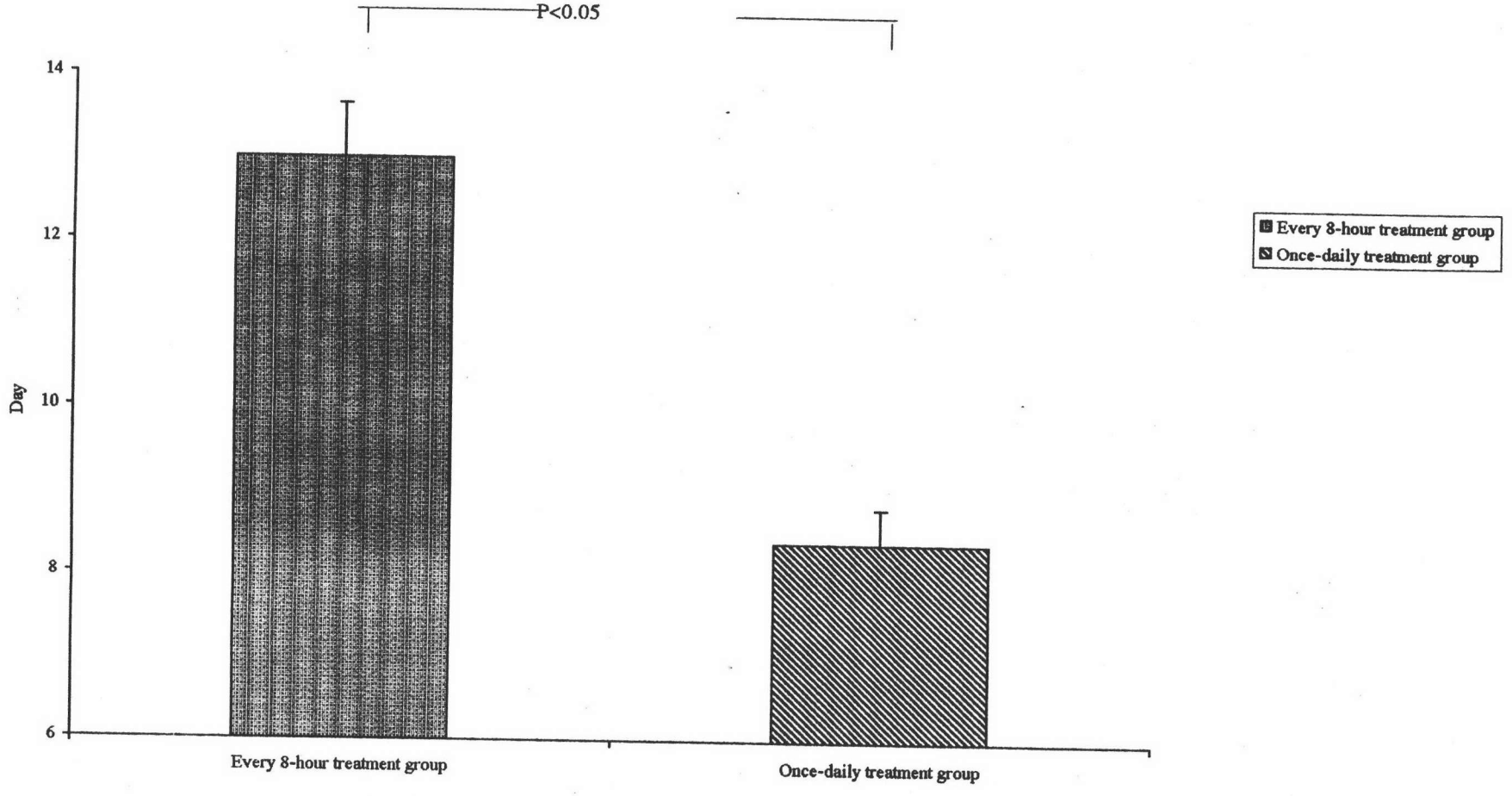
Continued.....

Every 8-hour treatment		Once-daily treatment	
No.	Duration	No.	Duration
17	-	17a	13
18	-	18a	3
19	7	19a	4
20	-	20a	8
21	-	21a	13
22	14	22a	12
23	13	23a	3
24	17	24a	5
25	9	25a	9
26	-	26a	9
27	14	27a	16
28	-	28a	8
29	-	29a	10
30	-	30a	8
31	-	31a	9
32	-	32a	-
33	10	33a	4
34	10	34a	3
35	11	35a	7
36	14	36a	11
37	12	37a	7
38	15	38a	14
39	14	39a	14
40	-	40a	14
41	20	41a	-
42	16	42a	-

Continued.....

Every 8-hourtreatment		Once-daily treatment	
No.	Duration	No.	Duration
43	23	43a	15
44	-	44a	17
45	15	45a	-
46	15	46a	-
Mean	13.2 ± 3.5	Mean	8.3 ± 4.0

Figure 4.13 Comparison duration of treatment between the every 8-hour treatment group and the once-daily treatment group



4. Nephrotoxicity

The criteria indicated the development of nephrotoxicity was serum creatinine increase for more than or equal to 0.5 mg/dl from the initial value. In the present study, 9 out of 46 (19.6%) of the patients in the every 8-hour treatment group showed signs of nephrotoxicity as compared to 5 out of 46 (16.9%) of the patients in the once-daily treatment group, as shown in table 4.7 and figure 4.14.

Figure 4.15 illustrated the change in serum creatinine from the initial value of the patients in the every 8-hour treatment group and the once daily treatment group. In this study, the serum creatinine of the patients in every 8-hour treatment group increased higher than those of the once-daily treatment since the 7th day (1.25 ± 0.16 mg/dl vs 1.02 ± 0.11 mg/dl) , the 9th day (1.20 + 0.30 mg/dl vs 0.96 + 0.26 mg/dl) , 11th (1.24 + 0.3 mg/dl vs 1.04 + 0.22 mg/dl) , the 13th day (1.28 + 0.26 mg/dl vs 1.05 + 0.13 mg/dl) , the 15th day (1.4 + 0.25 mg/dl vs 0.97 + 0.12) , the 17th day (1.43 + 0.25 mg/dl vs 1.1 + 0.2 mg/dl), $p < 0.001$.

Figure 4.16 displayed change of creatinine clearance from the initial value of the patients in both groups. There was significant difference in creatinine clearance decreasing caused by every 8-hour treatment as compared to once-daily treatment since the 7th day (58 + 2.3 vs 63.3 + 4.3 ml/min) , the 9th day(58.8 + 4.7 vs 60.9 ml/min) , the 11th day (52.3 + 5.6 vs 58.8 + 2.07 ml/min) , the 13rd day (51.3 + 3.7 vs 57.4 + 4.6 ml/min) , the 15th day (50.4 + 3.5 vs 56.5 + 4.2 ml/min) , the 17th day (49.5 + 3.7 vs 56.0 + 5.8 ml/min), $p < 0.05$.

The loading dose was calculated based on the patient's body weight, the appropriate dose was calculated by applying the Sarubbi and Hull method. The patients were excluded if the prescribed dosage ordered by the physicians was higher than 10% of the calculated appropriate dose. It was found that there was significant difference in creatinine clearance decrease between the two types of regimens for the patients with appropriate since the 15th day (54.0 + 5.5 vs 62.5 + 4.6 ml/min) , the 17th day (52.6 + 3.4 vs 62.7 + 5.8 ml/min) , ($p < 0.05$), as shown in figure

4.17. From the results of these , the occurance of nephrotoxicity will be decreased if the physician prescribes the appropriate dose calculated from body weight and applying the Sarubbi and Hull method. However, long term treatment of gentamicin, every 8-hour treatment has developed nephrotoxicity faster than once-daily treatment has.

There was no difference between the two groups of treatment in the occurrence of nephrotoxicity. However, the serum creatinine of the patients in the every 8-hour treatment group increased higher than the serum creatinine of the patients in the once-daily treatment group (figure 4.15) and the creatinine clearance of the patients in the every 8-hour treatment group decreased lower than the creatinine clearance of the patients in the once-daily treatment group. These results implied that there was development of nephrotoxicity in the every 8-hour treatment group. The nephrotoxicity may be reduced by closely monitoring serum gentamicin concentration and using pharmocokinetic parameters of individual patient to adjust his or her dosage regimen if the trough serum gentamicin concentration of the patient was over 2.0 mcg/ml or the serum creatinine increased more than 0.5 mg/dl from the initial value. The subjects participated in this study were too few and they were observed for a short period. If a larger group of patiens were observed and investigated for a long time, we might have found significant difference in nephrotoxicity between gentamicin treated every 8-hour treatment and gentamicin treated once-daily.

Table 4.7 Comparison nephrotoxicity between every 8-hour treatment and once-daily treatment.

Every 8- hour treatment		Once-daily treatment	
No.	Nephrotoxicity	No.	Nephrotoxicity
1	y	1a	y
2	y	2a	y
3	n	3a	n
4	n	4a	n
5	n	5a	n
6	n	6a	n
7	y	7a	n
8	y	8a	n
9	n	9a	n
10	n	10a	n
11	n	11a	n
12	n	12a	n
13	n	13a	n
14	n	14a	n
15	y	15a	n
16	n	16a	n
17	n	17a	n
18	n	18a	n
19	n	19a	n
20	n	20a	n
21	n	21a	n
22	n	22a	n
23	n	23a	n
24	n	24a	n
25	n	25a	n

Continued.....

Every 8- hour treatment		Once daily treatment	
No.	Nephrotoxicity	No.	Nephrotoxicity
26	n	26a	n
27	n	27a	n
28	n	28a	n
29	n	29a	n
30	n	30a	n
31	n	31a	n
32	n	32a	n
33	n	33a	n
34	n	34a	n
35	n	35a	n
36	n	36a	n
37	n	37a	n
38	n	38a	n
39	n	39a	y
40	n	40a	n
41	y	41a	n
42	n	42a	n
43	y	43a	y
44	y	44a	y
45	y	45a	n
46	n	46a	n
Total	9	Total	5
%	19.6	%	10.9

Figure 4.14 Comparison nephrotoxicity between the every 8-hour treatment group and the once-daily treatment group

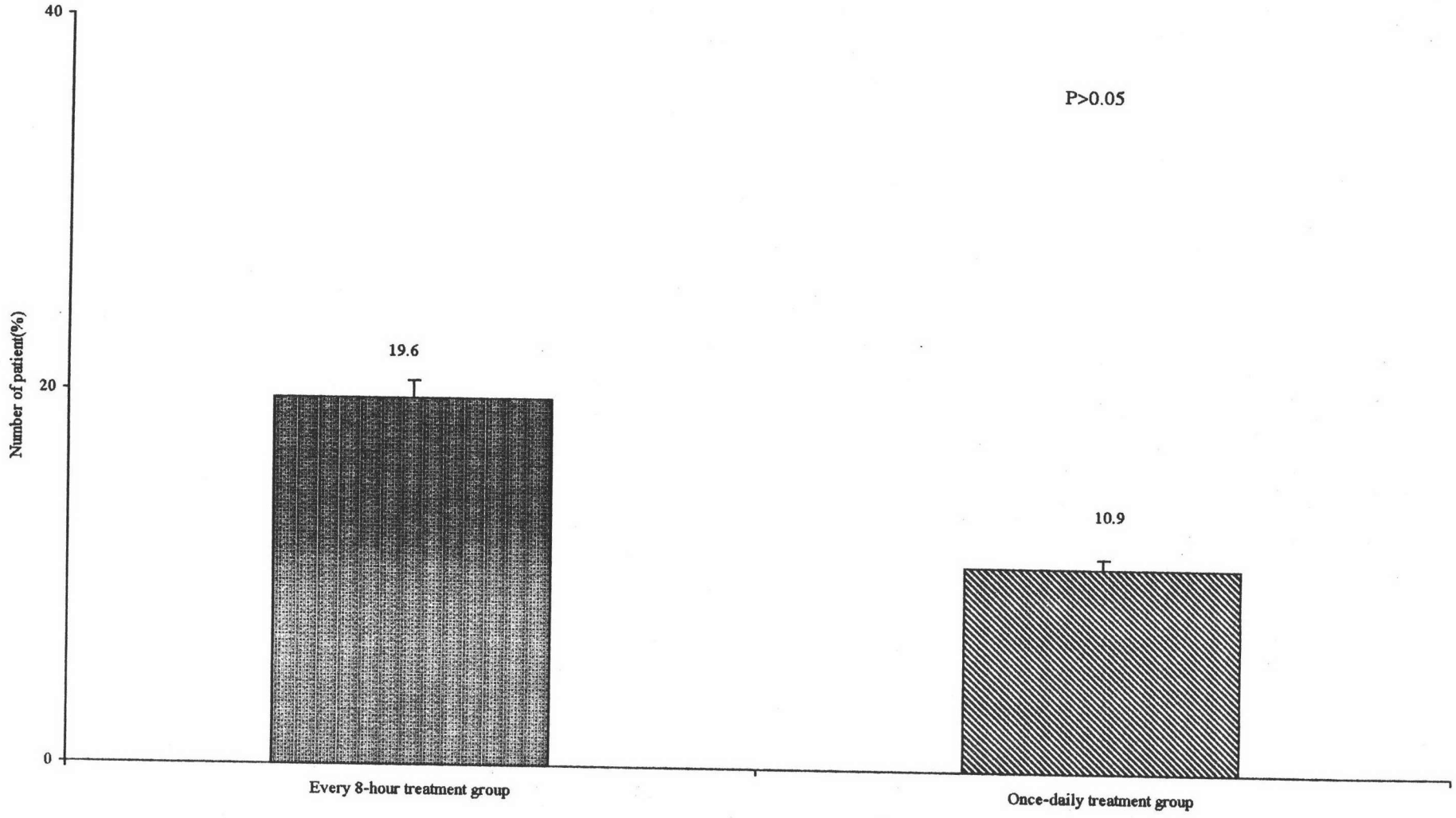


Figure 4.15 Comparison the change in serum creatinine of the every 8-hour treatment group and the once-daily treatment group

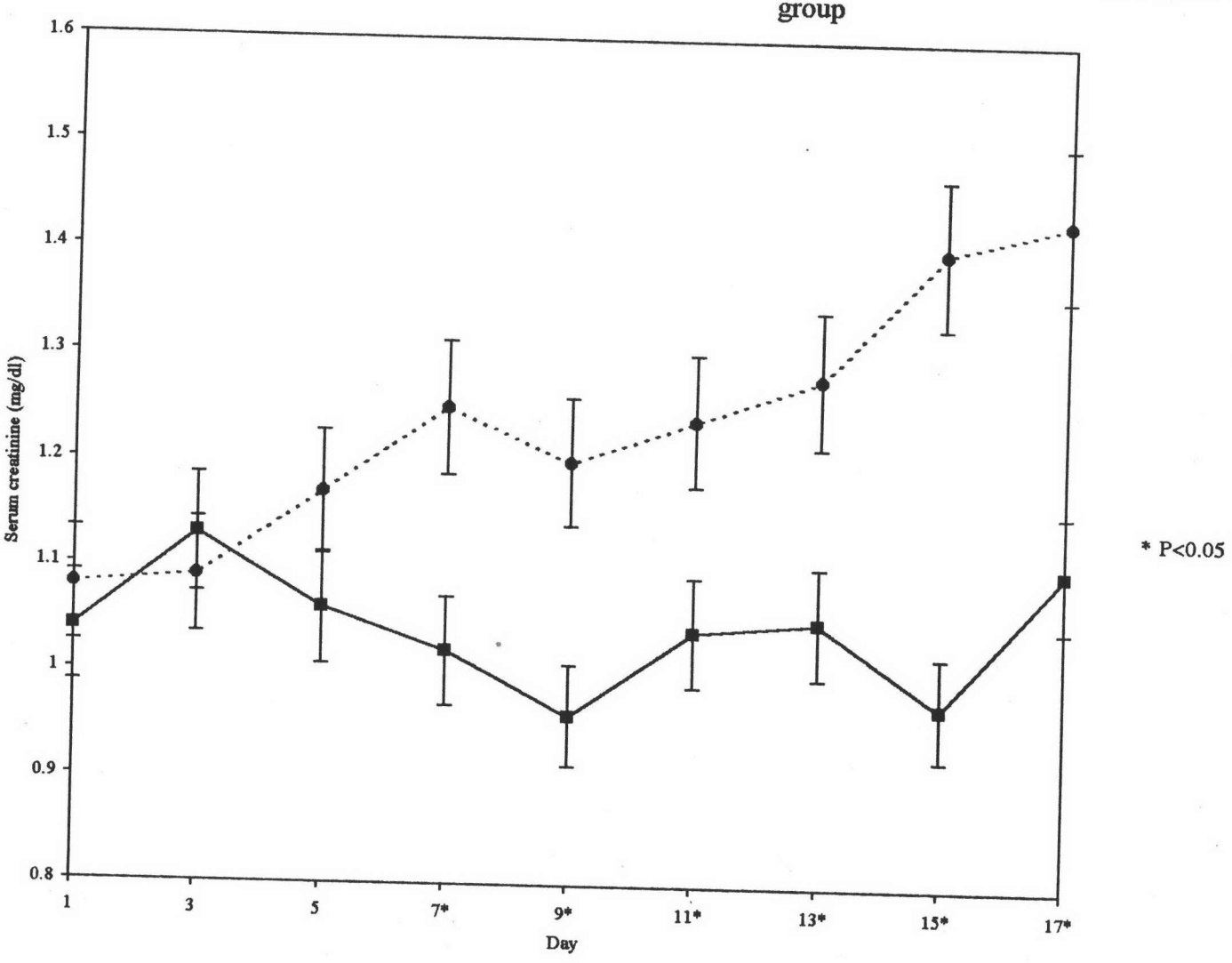


Figure 4.16 Comparison creatinine clearance decrement of the every 8-hour treatment group and the once-daily treatment group

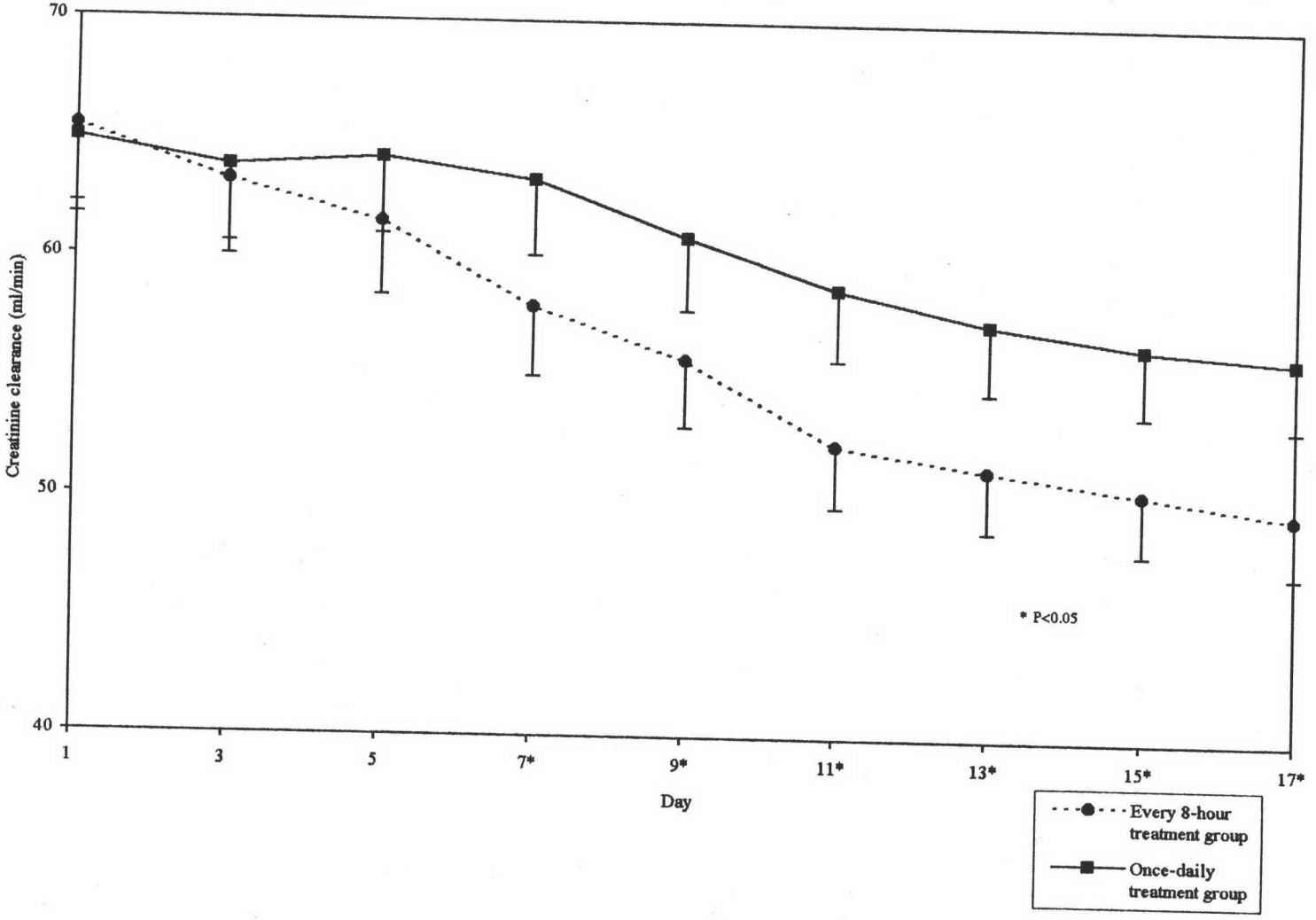
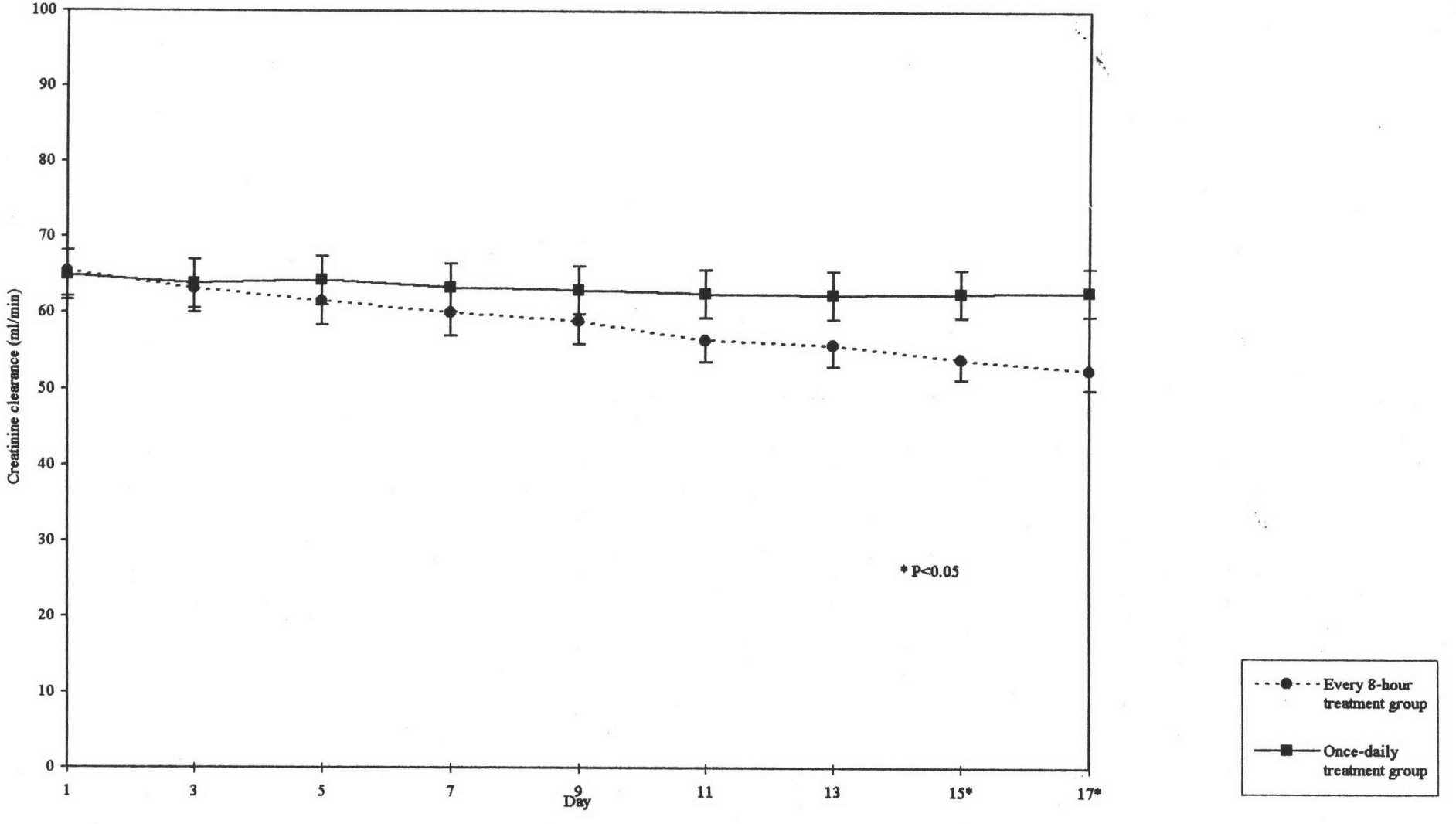


Figure 4.17 Comparison creatinine clearance decrement of the patients with appropriated dose in every 8-hour treatment group and once-daily treatment group.



5. Pharmacokinetic Data

The pharmacokinetic data are depicted in Table 4.8 and Table 4.9. Volume of distribution of the patients in every 8-hour treatment group were ranging from 6.7 to 39.6 (mean = 16.80, SD = 7.4 litres) and 5.0 to 21.2 (mean = 11.4, SD = 4.1 litres) for patients in once daily treatment group. There was no difference in distribution volume between two group of treatment, $p > 0.05$.

Elimination rate constant of every 8-hour treatment group ranging from 0.072 to 0.272 (mean = 0.162, SD = 0.056 per hour) and once daily treatment group ranging from 0.086 to 0.235 (mean = 0.169, SD = 0.052 per hour). There was no difference in elimination rate constant between two groups of treatment, $p > 0.05$.

There was no significant difference in half life of gentamicin between every 8-hour treatment group and once daily treatment group (4.9 ± 1.8 vs 4.6 ± 1.6, $p > 0.05$). This finding confirms that our matchings have no difference in pharmacokinetic parameters between the two groups of this study.

For Thai patients , the distribution volume , the elimination rate constant and the half-life were calculated from two groups of this study. The distribution volume of thai patient was 13.3 ± 5.6 litres while the distribution volume of foreign patient was 14.1 ± 5.8 litres (Darwin, 1994). The elimination rate constant of thai patient was 0.166 ± 0.054 per hour while the elimination rate constant of foreign patient was 0.20 ± 0.09 per hour (Darwin , 1994). The half-life of thai patient was 4.8 ± 1.7 hour while the half-life of foreign patient was 2.2 ± 2.1 hour (Darwin, 1994), as shown in table 4.10.

Table 4.11 shows the mean trough and peak serum gentamicin concentration between every 8-hour treatment group and once daily treatment group (mean trough = 1.7, SD = 0.6 vs mean trough = 0.5, SD = 0.5 and mean peak = 5.3, SD = 1.2 vs mean peak = 13.7, SD = 3.4).

Figure 4.18 presents the distribution of the peak and trough serum gentamicin concentration of the every 8-hour treatment group. The trough serum concentration were ranging from 0.5 to 4.2 mcg/ml and the peak serum concentration were ranging from 2.6 to 7.5 mcg/ml. Figure 4.19 shows the distribution of the peak and trough serum concentration of the once-daily treatment group. The trough serum concentration were ranging from 0.1 to 2.0 mcg/ml and the peak serum concentration were ranging from 5.8 to 19.6 mcg/ml. The peak serum concentration was very distributed so classification of the peak serum concentration by diseases could not be done. Diseases and problems in illness of the patients may cause the high distribution. The initial mean peak serum gentamicin concentrations in once daily treatment group was over therapeutic range , howevere , Cyrus Rustam Kumana and Kwok Yung Yuen (1994) mentioned that peak serum gentamicin concentration indicated efficacy rather than the risk of nephrotoxicity.

Table 4.12 and 4.13 classified patients by trough serum gentamicin concentration. In every 8-hour treatment group, nobody has trough serum concentration less than 0.5 mcg/ml. . Most of the patients (73.9%) have the trough serum concentration within the safety level (0.5-2.0 mcg/ml) and the other 26.1% were in toxic level (> 2.0 mcg/ml). For once-daily treatment group, there was little difference between the number of patients (45.7%) whose troug serum concentration were in safty level (0.5-1.0 mcg/ml) and those whose serum concentration were less than 0.5 mcg/ml (47.8%). Only 6.5% were in toxic level (> 1.0 mcg/ml).

Table 4.14 and 4.15 present the pharmacokinetic parameters and adjusted dose of the patients receiving every 8-hour treatment and once daily treatment whose the beggining dose were not appropriate and required a new regimen. There was no significant difference between predicted trough and measured trough in every 8-hour treatment group (mean = 1.8, SD = 0.17 vs mean = 2.1, SD = 0.5 mcg/ml , $p > 0.05$) but there was significant difference between predicted trough and measured trough serum gentamicin concentration in once daily treatment group (Mean = 0.85 , SD=0.07 vs mean = 1.0 ,SD = 0.12

mcg/ml , $p<0.05$). In once daily treatment group, peak and trough serum gentamicin of the patient number 82 was so high that could not be accurately estimated.

Table 4.16 shows creatinine clearance and appropriate dose of the patients compared to physician's prescribed dose. 30 patients in the every 8-hour treatment group and 43 patients in the once-daily treatment group were administrated by prescribed dose less than or equal to 10% of appropriate dose but 16 patients treated with every 8-hour treatment and 3 patients treated with once-daily treatment were given unappropriate dose. In unappropriate dose group , 7 patients in the every 8-hour treatment group developed nephrotoxicity while nobody in once-daily treatment group did. These results implied that the once-daily treatment was safe as compared to every 8-hour treatment and the occurrence of nephrotoxicity may be reduced if the patients were administrated by appropriate dose.

Figure 4.20 illustrated the overall result of gentamicin treatment. In safety level , the every 8-hour treatment group showed the number of the patients without nephrotoxicity (27 cases = 79 %) higher than the patients with nephrotoxicity (7 cases = 21%) and the once-daily treatment group showed the number of the patients without nephrotoxicity(39 cases = 91%) higher than the patients with nephrotoxicity (7 cases = 21%). In toxic level , the once daily-treatment group , 3 patients have the trough serum gentamicin concentration higher than 1.0 mcg/ml. 2 of them required new dosage regimens. After new dosage regimen administration , one patient with nephrotoxicity still had the trough serum gentamicin concentration higher than 1.0 mcg/ml but the other one without development of nephrotoxicity had the trough serum gentamicin concentration less than 1.0 mcg/ml. About the every 8-hour treatment group , 12 patients showed the trough serum gentamicin concentration higher than 2.0 mcg/ml. In this group, 10 patients required new dosage regimens. After new dosage regimen , the trough serum gentamicin concentrations were measured again to confirm the predicted trough serum gentamicin concentration. It was found that 7 patients were decreased the trough serum gentamicin concentration to less than or equal to 2.0 mcg/ml and all of them had no

development of nephrotoxicity. 3 patients still had the trough serum gentamicin concentration higher than 2.0 mcg/ml , 2 of them had development of nephrotoxicity while one patient had no development of nephrotoxicity. These findings indicated that incidence of nephrotoxicity may occur if the trough serum gentamicin concentration is higher than 2.0 mcg/ml for the every 8-hour treatment and 1.0 mcg/ml for the once-daily treatment and if the patient recieves new dosage regimen , the occurrence of nephrotoxicity may be decreased. For the previous recommendations, the trough serum gentamicin concentration less than or equal to 2.0 mcg/ml for the every 8-hour treatment and 1.0 mcg/ml for the once-daily treatment still had the least nephrotoxicity for gentamicin therapy.

From these results, once-daily treatment showed better efficacy and safety as compared to the every8-hour treatment. The trough concentration correlated well with nephrotoxicity , for the every 8-hour treatment group, the trough concentration sholud not be higher than 2.0 mcg/ml while the trough concentration of the once-daily treatment group should not be higher than 1.0 mcg/ml.

Table 4.8 Pharmacokinetic data of patients with every 8-hour treatment.

No	IBW	P.dose	Cp	Ct	Kd	T1/2	Vd
1	47.7	60.0	5.7	2.5	0.118	5.9	15.3
2	50.5	60.0	4.4	1.2	0.186	3.7	14.6
3	49.6	50.0	5.2	2.3	0.117	5.9	14.1
4	52.3	40.0	4.8	1.7	0.148	4.7	10.3
5	43.2	50.0	4.8	1.2	0.198	3.5	10.7
6	52.3	80.0	4.8	2.1	0.118	5.9	24.2
7	50.5	60.0	3.6	1.7	0.107	6.5	26.0
8	47.7	60.0	4.1	1.8	0.118	5.9	21.3
9	47.7	40.0	4.6	2.4	0.093	7.5	15.1
10	49.6	40.0	6.8	2.1	0.168	4.1	6.7
11	49.6	60.0	3.8	2.0	0.092	7.6	27.7
12	47.7	60.0	7.5	1.5	0.230	3.0	7.6
13	52.3	70.0	6.9	1.2	0.250	2.8	9.1
14	66.4	60.0	3.2	0.5	0.265	2.6	16.3
15	66.4	60.0	7.5	4.2	0.083	8.4	15.2
16	66.4	70.0	4.0	2.1	0.092	7.5	30.6
17	47.7	60.0	3.8	2.0	0.092	7.6	27.7
18	56.8	60.0	4.8	2.2	0.111	6.2	19.0
19	54.1	60.0	4.8	2.1	0.118	5.9	18.2
20	70.9	60.0	3.2	0.5	0.265	2.6	16.3
21	61.8	60.0	4.9	1.4	0.179	3.9	13.5
22	47.7	70.0	6.7	1.0	0.272	2.6	9.0
23	49.6	60.0	5.4	1.2	0.215	3.2	10.9
24	66.4	90.0	5.8	1.1	0.238	2.9	14.4
25	50.5	60.0	3.9	1.7	0.119	5.8	22.3
26	47.7	60.0	4.8	1.2	0.198	3.5	12.9
27	47.7	60.0	7.2	1.5	0.224	3.1	8.0
28	47.7	60.0	4.8	1.6	0.157	4.4	14.9
29	63.7	60.0	5.3	1.8	0.154	4.5	13.7

Continued.....

No	IBW	P.dose	Cp	Ct	Kd	T1/2	Vd
30	56.8	60.0	4.8	2.6	0.088	7.9	22.7
31	61.4	60.0	5.1	1.8	0.149	4.7	14.6
32	52.3	60.0	4.5	1.4	0.167	4.2	15.3
33	47.7	70.0	4.8	1.1	0.210	3.3	14.5
34	52.3	60.0	6.7	1.4	0.224	3.1	8.6
35	59.1	50.0	5.6	1.3	0.209	3.3	8.9
36	66.4	80.0	5.8	1.3	0.214	3.2	13.6
37	66.4	50.0	4.8	1.2	0.198	3.5	10.7
38	52.3	80.0	4.8	1.7	0.148	4.7	20.7
39	47.7	80.0	4.3	2.6	0.072	9.6	39.6
40	45.9	70.0	4.3	1.6	0.141	4.9	20.9
41	50.5	60.0	5.1	1.8	0.149	4.7	14.6
42	61.8	60.0	5.5	1.2	0.217	3.2	10.6
43	66.4	50.0	3.7	0.9	0.202	3.4	13.8
44	66.4	50.0	3.0	1.4	0.109	6.4	25.7
45	66.4	60.0	2.6	1.2	0.110	6.3	35.2
46	70.9	80.0	6.0	2.4	0.130	5.3	18.1
average	55.3	61.3	5.3	1.7	0.162	4.9	16.8
sd	8.1	10.7	1.2	0.6	0.056	1.8	7.4
max	70.9	90.0	7.5	4.2	0.272	9.6	39.6
min	43.2	40.0	2.6	0.5	0.072	2.6	6.7

Table 4.9 Pharmacokinetic data of patients with once daily treatment.

No	IBW	P.dose	Cp	Ct	Kd	T1/2	Vd
1a	50.5	200.0	14.2	0.9	0.123	5.7	12.4
2a	47.7	160.0	10.4	1.5	0.086	8.1	15.5
3a	49.6	180.0	17.9	0.1	0.231	3.0	7.1
4a	52.3	100.0	10.2	0.4	0.144	4.8	8.2
5a	47.7	120.0	12.5	0.1	0.215	3.2	7.0
6a	54.1	240.0	18.9	0.2	0.202	3.4	9.5
7a	56.8	160.0	11.5	0.1	0.211	3.3	10.2
8a	47.7	160.0	12.9	1.8	0.088	7.9	12.4
9a	49.6	120.0	17.0	0.1	0.228	3.0	5.0
10a	47.7	120.0	5.8	0.8	0.088	7.9	20.6
11a	52.3	160.0	12.9	0.7	0.130	5.4	10.7
12a	52.3	180.0	18.3	0.8	0.139	5.0	8.3
13a	52.3	160.0	19.6	0.1	0.235	3.0	5.8
14a	66.4	160.0	14.0	0.6	0.140	5.0	9.6
15a	61.8	160.0	14.9	0.1	0.222	3.1	7.7
16a	66.4	240.0	17.6	0.1	0.230	3.0	9.7
17a	52.3	160.0	10.4	0.8	0.114	6.1	13.9
18a	52.3	200.0	14.9	2.0	0.089	7.8	13.3
19a	54.1	240.0	11.5	0.1	0.211	3.3	15.3
20a	66.4	200.0	18.5	0.1	0.232	3.0	7.7
21a	66.4	160.0	9.7	0.1	0.203	3.4	12.3
22a	50.5	180.0	10.5	0.1	0.207	3.4	12.7
23a	47.3	140.0	15.2	0.5	0.152	4.6	7.5
24a	66.4	240.0	13.2	1.0	0.115	6.0	16.4
25a	49.6	160.0	10.2	0.7	0.119	5.8	13.9
26a	52.3	160.0	11.9	0.1	0.212	3.3	9.8

Continued.....

No	IBW	Ord.dose	Cp	Ct	Kd	T1/2	Vd
27a	47.7	150.0	15.0	0.8	0.130	5.3	8.6
28a	52.3	240.0	17.6	0.1	0.230	3.0	9.7
29a	70.9	140.0	7.7	0.6	0.113	6.1	16.4
30a	52.3	200.0	14.2	0.1	0.220	3.1	10.2
31a	66.4	200.0	9.6	0.5	0.131	5.3	17.9
32a	47.7	160.0	10.5	0.9	0.109	6.3	14.0
33a	52.3	160.0	19.6	0.1	0.235	3.0	5.8
34a	52.3	160.0	14.9	0.6	0.143	4.9	9.0
35a	66.4	200.0	13.2	0.1	0.217	3.2	11.0
36a	66.4	240.0	9.9	0.6	0.125	5.6	21.2
37a	66.4	160.0	17.0	0.1	0.228	3.0	6.7
38a	52.3	240.0	10.5	0.7	0.120	5.8	20.2
39a	49.6	240.0	18.6	0.8	0.140	5.0	10.8
40a	52.3	210.0	9.7	0.1	0.203	3.4	16.1
41a	52.3	200.0	13.2	0.1	0.217	3.2	11.0
42a	66.4	200.0	13.6	0.1	0.218	3.2	10.7
43a	66.4	180.0	15.7	0.8	0.132	5.2	9.8
44a	66.4	150.0	14.6	0.9	0.124	5.6	9.0
45a	61.8	160.0	18.5	0.1	0.232	3.0	6.1
46a	57.3	240.0	11.9	0.6	0.133	5.2	17.2
average	56.1	180.2	13.7	0.5	0.169	4.6	11.4
sd	7.5	38.0	3.4	0.5	0.052	1.6	4.1
max	70.900	240.000	19.600	2.000	0.235	8.053	21.174
min	47.300	100.000	5.800	0.100	0.086	2.954	5.033

Table 4.10 Pharmacokinetic parameters of gentamicin treatment for Thai patient compare to foreign patient.

PHARMACOKINETIC PARAMETERS	FOREIGN PATIENT	THAI PATIENT
Distribution Volume (litre)	13.3 ± 5.6	14.1 ± 5.8
Elimination Rate Constance (per hour)	0.20 ± 0.09	0.166 ± 0.054
Half-Life (hour)	2.2 ± 2.1	4.8 ± 1.7

Pharmacokinetic parameters for foreign patient (Darwin , 1994).

Table 4.11 Comparison of trough and peak serum gentamicin concentration between every 8 hours treatment and once daily treatment.

Every 8-hourstreatment			Once-daily treatment		
No.	trough (mcg/ml)	Peak (mcg/ml)	No.	trough (mcg/ml)	Peak (mcg/ml)
1	2.5	5.7	1a	0.9	14.2
2	1.2	4.4	2a	1.5	10.4
3	2.3	5.2	3a	0.1	17.9
4	1.7	4.8	4a	0.4	10.2
5	1.2	4.8	5a	0.1	12.5
6	2.1	4.8	6a	0.2	18.9
7	1.7	3.6	7a	0.1	11.5
8	1.8	4.1	8a	1.8	12.9
9	2.4	4.6	9a	0.1	17.0
10	2.1	6.8	10a	0.8	5.8
11	2.0	3.8	11a	0.7	12.9
12	1.5	7.5	12a	0.8	18.3
13	1.2	6.9	13a	0.1	19.6
14	0.5	3.2	14a	0.6	14.0
15	4.2	7.5	15a	0.1	14.9
16	2.1	4.0	16a	0.1	17.6
17	2.0	3.8	17a	0.8	10.4
18	2.2	4.8	18a	2.0	14.9
19	2.1	4.8	19a	0.1	11.5
20	0.5	3.2	20a	0.1	18.5

Continued.....

Every 8-hour treatment			Once-daily treatment		
No.	trough (mcg/ml)	Peak (mcg/ml)	No.	trough (mcg/ml)	Peak (mcg/ml)
21	1.4	4.9	21a	0.1	9.7
22	1.0	6.7	22a	0.1	10.5
23	1.2	5.4	23a	0.5	15.2
24	1.1	5.8	24a	1.0	13.2
25	1.7	3.9	25a	0.7	10.2
26	1.2	4.8	26a	0.1	11.9
27	1.5	7.2	27a	0.8	15.0
28	1.6	4.8	28a	0.1	17.6
29	1.8	5.3	29a	0.6	7.7
30	2.6	4.8	30a	0.1	14.2
31	1.8	5.1	31a	0.5	9.6
32	1.4	4.5	32a	0.9	10.5
33	1.1	4.8	33a	0.1	19.6
34	1.4	6.7	34a	0.6	14.9
35	1.3	5.6	35a	0.1	13.2
36	1.3	5.8	36a	0.6	9.9
37	1.2	4.8	37a	0.1	17.0
38	1.7	4.8	38a	0.7	10.5
39	2.6	4.3	39a	0.8	18.6
40	1.6	4.3	40a	0.1	9.7
41	1.8	5.1	41a	0.1	13.2

Continued.....

Every 8-hour treatment			Once-daily treatment		
No.	trough (mcg/ml)	Peak (mcg/ml)	No.	trough (mcg/ml)	Peak (mcg/ml)
42	1.2	5.5	42a	1.0	13.6
43	0.9	3.7	43a	0.8	15.7
44	1.4	3.0	44a	0.9	14.6
45	1.2	2.6	45a	0.1	18.5
46	2.4	6.0	46a	0.6	11.9
Mean	1.7 ± 0.6	5.3 ± 1.2	Mean	0.5 ± 0.5	13.7 ± 3.4

Figure 4.18 The peak and trough serum gentamicin concentration of the patients in the every 8-hour treatment group.

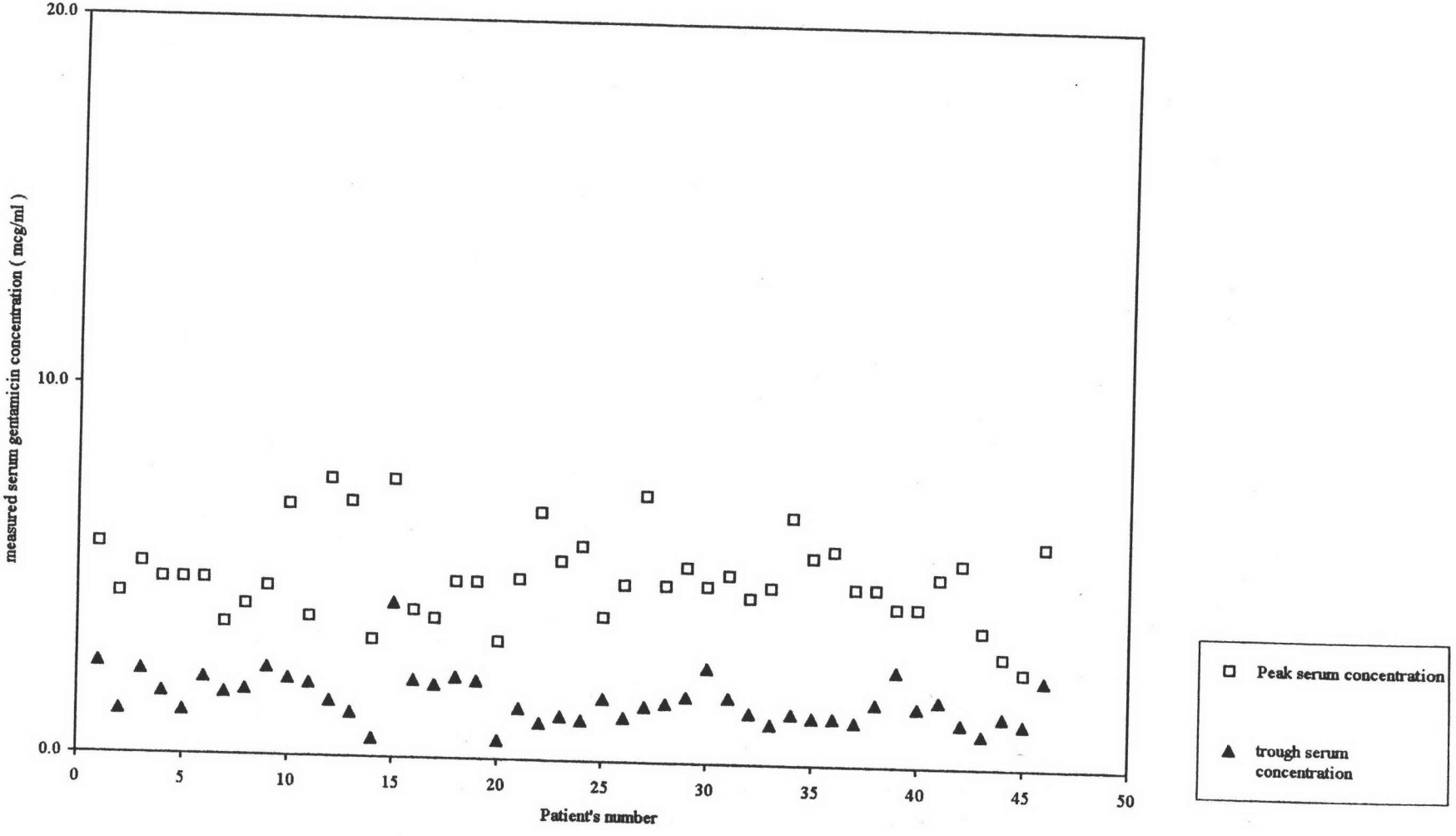


Figure 4.19 The peak and trough serum gentamicin concentration of the patients in the once-daily treatment group.

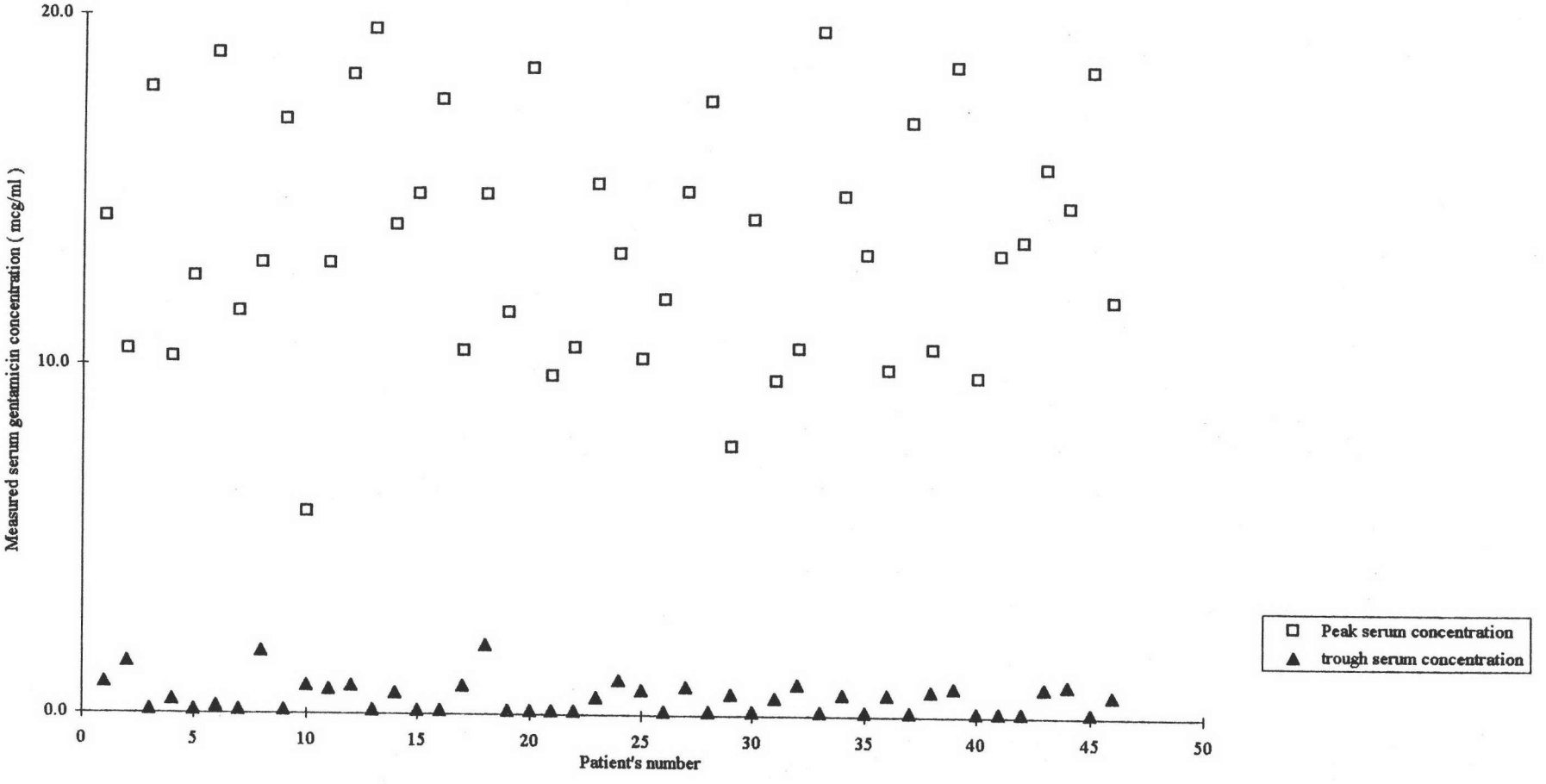


Table 4.12 Classification of patients with every 8 hours treatment by trough serum gentamicin concentration.

Trough serum concentration (mcg/ml)	Number of patients (persons)	Percentage (%)
< 0.5	0	0
0.5-2.0	34	73.9
> 2.0	12	26.1
Total	46	100.0

Table 4.13 Classification of patients with once daily treatment by trough serum gentamicin concentration.

Trough serum concentration (mcg/ml)	Number of patients (persons)	Percentage (%)
< 0.5	22	47.8
0.5-1.0	21	45.7
> 1.0	3	6.5
Total	46	100.0

Table4.14 Pharmacokinetic parameters and the adjusted dose of the patient with every 8-hour treatment who have new regimen.

No	Cp	Ct	Cr_s	Kd	$T_{1/2}$	Vd	Cdt	Dose	Cal. dose	Adj. dose	Ctexp.	Ctmeas.
1	5.7	2.5	3.2	0.118	5.9	15.3	1.5	60	36	40	1.7	2.1
2	6.8	2.9	1.5	0.122	5.7	12.5	1.5	60	33.2	40	1.9	2.0
3	5.2	2.3	1.4	0.117	5.9	14.0	1.5	50	32.6	40	1.8	2.0
6	4.8	2.4	1.7	0.099	7.0	27.6	1.5	80	33.3	50	1.5	1.3
7	5.9	2.8	1.4	0.106	6.5	16.1	1.5	60	32.3	40	1.9	2.2
8	6.3	2.8	1.4	0.116	6.0	14.0	1.5	60	32.2	40	1.9	2.0
15	7.5	4.2	1.4	0.083	8.3	15.2	1.5	60	21.5	30	2.1	3.1
16	4.0	2.1	1.3	0.092	7.5	30.7	1.5	70	50.0	50	1.5	1.7
18	4.8	2.2	1.4	0.112	6.2	18.8	1.5	60	41.0	40	1.5	2.0
19	4.8	2.1	1.6	0.118	5.9	18.2	1.7	60	48.6	50	1.7	1.8
25	5.8	2.8	1.9	0.104	6.7	16.5	1.8	60	38.5	40	1.9	2.4
30	4.8	2.6	1.0	0.088	7.9	22.6	1.7	60	39.2	40	1.7	2.1
32	6.9	2.8	1.4	0.129	5.4	11.9	1.8	60	40.5	40	1.8	2.3
39	4.3	2.6	1.5	0.072	9.6	39.5	1.8	80	55.4	60	1.9	2.0
40	6.6	4.2	1.7	0.065	10.7	36.9	1.8	70	45.2	50	2.0	3.5
41	6.4	2.6	1.3	0.129	5.4	12.8	1.8	60	41.5	40	1.7	2.2
43	5.3	2.3	2.1	0.119	5.8	13.7	1.8	50	39.1	40	1.8	2.0
44	3.3	2.4	1.7	0.045	15.4	48.2	1.8	50	37.5	40	1.9	2.1
46	6.0	2.4	1.4	0.130	5.3	18.2	1.8	80	60	60	1.8	1.9

Table 4.15 Presents the pharmacokinetic parameters and adjusted dose of the patient with once daily treatment who have new regimen.

No	Cp	Ct	Cr_s	Kd	$T_{1/2}$	Vd	Ct	Dose	Cal. dose	Adj. dose	Ctexp.	Ctmeas.
1a	17.6	1.9	1.8	0.099	7.0	11.6	0.9	200	94.8	100	0.9	1.1
2a	10.4	1.5	1.1	0.086	8.1	15.5	0.7	160	74.6	80	0.75	0.8
8a	12.9	1.8	1.7	0.088	7.9	12.2	0.8	160	70.9	70	0.8	1.1
39a	22.2	5.2	1.5	0.064	10.8	12.6	1.0	240	46.2	140*	0.8	2.8
43a	16.5	1.6	1.0	0.104	6.7	10.1	0.8	180	90	100	0.9	1.0
44a	15.8	1.3	1.6	0.11	6.2	8.7	0.8	150	92.5	100	0.9	1.0

Table 4.16 Creatinine clearance and appropriated dose of patients compared to presclibed dose.

No	IBW (kg)	Cl_{cr}	Loa. dose	Ap. dose *10 %	Ap. dose	Prib. dose	No	IBW (kg)	Cl_{cr}	Loa. dose	Ap. dose	Ap. dose*10%	Prib. dose
1	47.7	35.0	90	47	51.7	60	1a	50.5	30.5	240	207	288	200
2	50.5	72.2	101	78	85.8	60	2a	47.7	90.2	239	239	268	160
3	49.6	28.4	66	31	34.1	50	3a	49.6	20.3	215	162	178	180
4	52.3	40.7	94	54	59.4	40	4a	52.3	45.2	200	192	211	100
5	43.2	39.5	87	49	53.9	50	5a	47.7	34.7	239	212	233	120
6	52.3	40.7	105	60	66	80	6a	54.1	62.7	271	271	298	240
7	50.5	42.5	90	53	58.3	60	7a	56.8	41.3	200	186	205	160
8	47.7	48.3	92	59	64.9	60	8a	47.7	30.9	205	177	195	160
9	47.7	32.5	80	40	44.0	40	9a	49.6	29.0	205	174	191	120
10	49.6	19.1	84	22	24.2	40	10a	47.7	21.6	225	173	190	120
11	49.6	24.1	99	42	46.2	60	11a	52.3	34.2	250	221	243	160
12	47.7	41.4	78	45	49.5	60	12a	52.3	21.0	210	160	176	180
13	52.3	43.8	105	63	69.3	70	13a	52.3	49.4	261	260	286	160
14	66.4	107.2	124	124	136	60	14a	66.4	73.6	265	265	292	160
15	66.4	85.2	96	79	86.9	60	15a	61.8	55.0	210	210	231	160
16	66.4	95.6	106	106	117	70	16a	66.4	128.1	300	300	330	240
17	47.7	34.7	90	47	51.7	60	17a	52.3	57.8	210	210	231	160
18	56.8	56.8	114	79	86.9	60	18a	52.3	35.6	261	234	257	200
19	54.1	48.1	108	69	75.9	60	19a	54.1	90.2	271	271	298	240
20	70.9	103.3	124	124	136	60	20a	66.4	111.7	325	235	259	200
21	61.8	97.2	120	120	132	60	21a	66.4	73.2	290	290	319	160

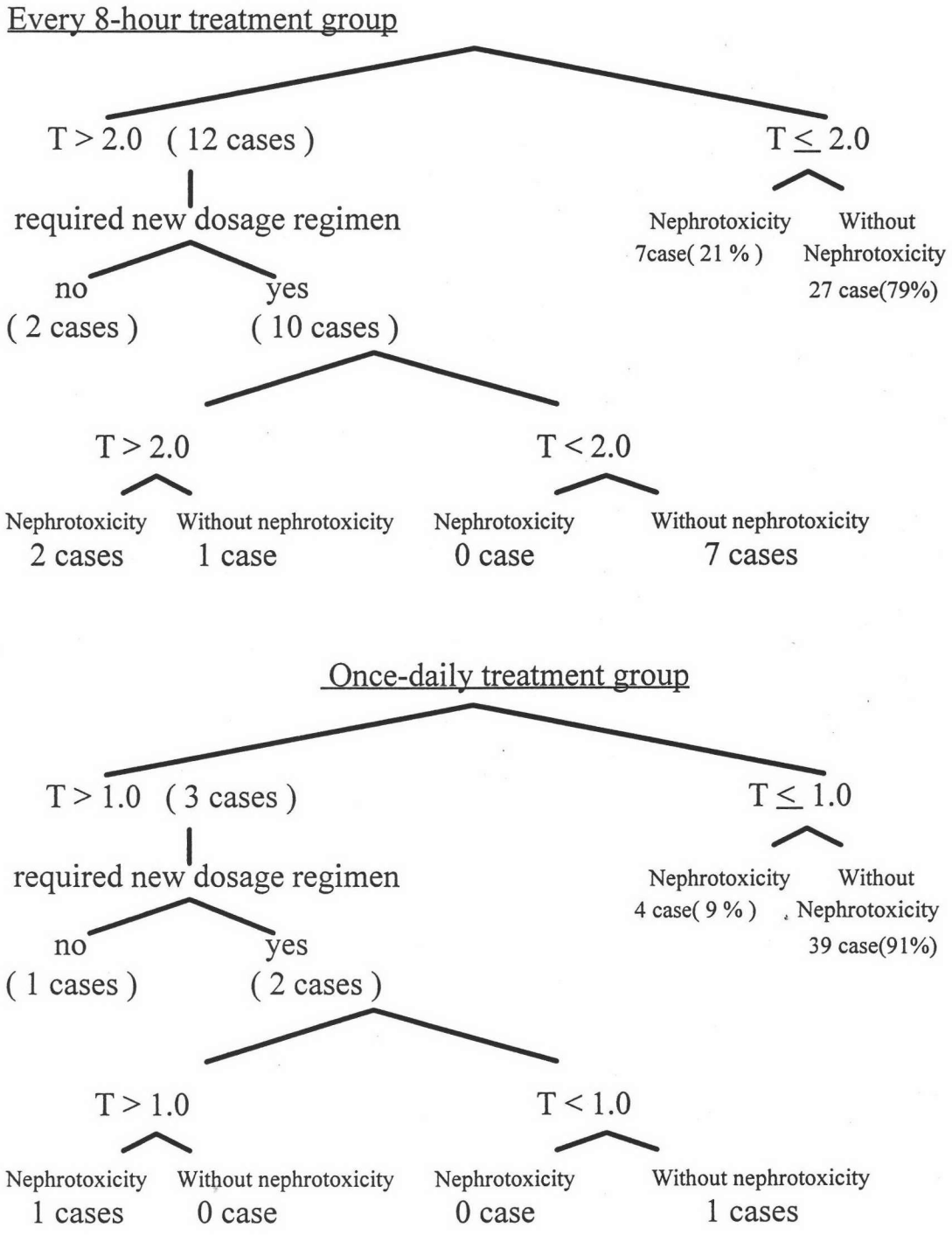
Continued.....

No	IBW (kg)	Cl_{cr}	Loa. dose	Ap. dose	Ap. dose *10 %	Prib dose	No	IBW (kg)	Cl_{cr}	Loa. dose	Ap. dose	Ap. dose *10 %	Prib . dose
22	47.7	46.0	90	56	61.6	70	22a	50.5	41.9	210	196	216	180
23	49.6	41.9	96	56	61.6	60	23a	47.3	19.6	180	134	147	140
24	66.4	89.1	133	111	122	90	24a	66.4	108.3	300	300	330	240
25	50.5	26.2	90	40	44	60	25a	49.6	18.1	200	144	158	160
26	47.7	39.6	90	51	56.1	60	26a	52.3	36.2	210	188	207	160
27	47.7	77.9	84	67	73.7	60	27a	47.7	65.0	190	190	209	150
28	47.7	68.2	84	63	69.3	60	28a	52.3	87.2	261	261	287	240
29	63.7	39.1	84	47	51.7	60	29a	70.9	35.5	175	156	172	140
30	56.8	100.6	114	114	125	60	30a	52.3	94.1	261	261	287	200
31	61.4	112.8	123	123	135	60	31a	66.4	92.2	332	332	365	200
32	52.3	56.1	88	60	66	60	32a	47.7	72.4	190	190	209	160
33	47.7	50.7	96	63	69.3	70	33a	52.3	58.9	210	210	231	160
34	52.3	43.7	105	63	69.3	60	34a	52.3	30.1	261	225	248	160
35	59.1	78.0	108	86	94.6	50	35a	66.4	93.4	275	275	303	200
36	66.4	73.8	133	103	113	80	36a	66.4	118.8	332	332	365	240
37	66.4	42.5	90	53	58.3	50	37a	66.4	51.4	275	275	303	160
38	52.3	55.7	104	71	78.1	80	38a	52.3	89.3	250	250	275	240
39	47.7	52.9	96	64	70.4	80	39a	49.6	101.1	248	248	273	240
40	45.9	81.3	92	74	81.4	70	40a	52.3	56.6	261	261	287	210
41	50.5	66.3	89	66	72.6	60	41a	52.3	72.0	261	261	287	200
42	61.8	38.7	100	56	61.6	60	42a	66.4	95.3	280	280	308	200
43	66.4	48.5	108	69	75.9	50	43a	66.4	88.1	285	285	314	180

Cotinued.....

No	IBW (kg)	Cl_{cr}	Loa. dose	Ap. dose	Ap. dose *10%	Ord. dose	No	IBW (kg)	Cl_{cr}	Loa. dose	Ap. dose	Ap. dose *10 %	Ord. dose
44	66.4	90.3	100	100	110	50	44a	66.4	63.9	235	235	259	150
45	66.4	86.0	110	91	100	60	45a	61.8	54.9	255	255	281	160
46	70.9	100.8	140	140	154	80	46a	57.3	87.5	286	286	315	240

Figure 4.20 Over all clinical response of gentamicin treatment.



3.2 The once-daily treatment has shown decrease of creatinine clearance in the patients given appropriate dose and non appropriate dose less than the every 8-hour treatment.

3.4 For long term treatment of gentamicin , the every 8-hour treatment has developed nephrotoxicity faster than once-daily treatment.

4. Pharmacokinetic parameters.

4.1 There were no significant difference in the distribution volume , the elimination rate constant and the half-life of gentamicin between the foreign patients and Thai patients , $p < 0.05$.

4.2 Most patients in both groups of treatment have presented the trough serum gentamicin concentration in safety level but number of patient whose trough serum concentration was in toxic level in the every 8-hour treatment group were higher than in the once-daily treatment group.

4.3 The occurrence of nephrotoxicity may decrease if the patients are given the appropriate dose at first time.

4.4 The incidence of nephrotoxicity may occur if the trough serum gentamicin concentration is higher than 2.0 mcg/ml for the every 8-hour treatment and 1.0 mcg/ml for the once-daily treatment and if the patiens were closely monitored the trough serum gentamicin concentration and adjusted dosage regimen, the occurrence of nephrotoxicity will be decreased.

4.5 The trough concentration correlated well with nephrotoxicity, for the every 8-hour treatment group, the trough concentration should not be higher than 2.0 mcg/ml while the trough concentration of the once-daily treatment group should not be higher than 1.0 mcg/ml.